NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sapropterin for treating phenylketonuria [ID1475]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Sapropterin for treating phenylketonuria [ID1475]

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document from BioMarin**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. British Inherited Metabolic Diseases Group
   b. Royal College of Physicians
   c. National Society for Phenylketonuria
      i. Appendices of responses

4. **Comments on the Appraisal Consultation Document from experts:**
   a. Prof. Anita MacDonald, Consultant Dietitian – clinical expert, nominated by the National Society for Phenylketonuria and the British Dietetic Association
   b. Dr Hugh Lemonde, Consultant Paediatric Inherited Metabolic Disease – clinical expert, nominated by the British Inherited Metabolic Disease Group
   c. Dr Robin Lachmann, Consultant in Metabolic Medicine – clinical expert, nominated by the Royal College of Physicians
   d. Sharon Buckley, Patient Advocate – patient expert, nominated by the National Society for Phenylketonuria
   e. Patient expert, nominated by the National Society for Phenylketonuria

5. **Comments on the Appraisal Consultation Document received through the NICE website**

6. **Comments on the Appraisal Consultation Document from members of the public and MPs**

7. **Evidence Review Group critique of company comments on the ACD**
   a. ERG additional analyses 0 to 25 years
   b. ERG additional analyses 21 to 25 years

8. **Thematic analysis of consultation comments**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Appraisal title

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Stakeholder comment	NICE Response Please respond to each comment
Themes arising from thematic review undertaken from all stakeholder, public and web comments received **1) Stopping treatment with sapropterin at 18 years of age (92% of all 401 responses)** Respondents disagreed, questioned or expressed concerns about the decision to stop treatment with sapropterin at 18. Respondents described the decision to stop treatment at 18 as disruptive, unfair, unethical, dangerous, irresponsible, or distressing to young adults. Respondents suggested that treatment with sapropterin should be continued after 18 because PKU is 'for life' and so is the PKU diet according to clinical practice. Some respondents highlighted that they would not start sapropterin treatment for their children at all to avoid disruption and distress to their children's lives when reaching adulthood. Respondents indicated that sapropterin should be available for adults: • Up to 25 years of age • For life Respondents indicated that children lose the support of their parents and/or carers which leads to difficulties in managing the PKU diet on their own. Because of this and responsibilities of adulthood, managing the PKU diet becomes more difficult. Respondents highlighted that stopping treatment with sapropterin at 18 will be challenging because: • Having lived all their life with the liberties and unrestricted diet that come with sapropterin treatment, young adults would have to learn how to manage the PKU diet from scratch with no experience or coping skills, which are normally developed during childhood and throughout teenage years. • Young adults may not be able to adhere to or manage the PKU diet due to a lack the lack of skills and coping mechanisms usually formed during childhood and teenage years. • Young adults may not be able to establish blood Phe control through dietary treatment, leading to PKU symptoms and potentially reducing their ability to manage the PKU diet. • Young adults will not be accustomed to the taste or smell of the PKU diet and will have to adjust to tolerate low protein foods and protein substitutes. • Young adults are transitioning from children to adult clinical services, which are not equipped to educate adults or teach and instil the necessary skills to manage the PKU diet. Respondents highlighted that stopping treatment with sapropterin is likely to lead to additional demands on the healthcare system to: • Support people with PKU to manage the mental health effects of high Phe levels. • Support and educate people with PKU on how to manage the PKU diet. • Support people with PKU to achieve blood Phe control and reduce PKU symptoms Respondents highlighted that stopping treatment with sapropterin will have a substantial impact on young adults' abilities to: • Live independently away from their parents' home. • Manage higher education studies. • Start and manage apprenticeships or jobs. • Undertake final exams and leave school. • Join and socialise with their peers. • Form personal relationships. • Start a family. Additionally, respondents also indicated that stopping treatment will have a detrimental impact on young adults': • Brain development	Comments noted. The committee considered the responses to the ACD on this theme and comments made during the committee meeting, and the guidance document has been updated. See section 1.1 of the FAD The committee recognised that stopping treatment and relying on diet alone at 18 years old is not ideal. It would benefit young adults if treatment with sapropterin could be continued for as long as possible during final brain development and transition into adulthood. The maximum age at which sapropterin can be considered a cost-effective use of NHS resources is 21. However, for this to be cost effective people would need to continue the dose they were having when they were under 18. In practice this may mean that some young adults may need more dietary control alongside sapropterin between the ages of 18 and 21 than they would with a higher dose. See sections 3.6, 3.30, 3.34, 3.36 and 3.38 of the FAD.

Stakeholder comment	NICE Response Please respond to each comment
• Quality of life	
2) Occurrence of brain damage in adults (70% of all 401 responses) Respondents highlighted that NICE's statements about brain damage in adults are contradictory and that they do not agree with NICE's conclusions. Respondents felt that: • Patients with brain damage because of late diagnosis or because they had been advised to come off diet were being forgotten. • NICE ignored that the brain does not stop changing or developing throughout life. Respondents indicated that brain development continues: • In early adulthood • Until 25 years of age or beyond Respondents highlighted that brain damage occurs even in people with early-treated PKU and manifests as: • Cognitive impairments • Reduced executive function • Deteriorating mental health • Reductions in white matter • Grey matter abnormalities • Lower IQ scores than expected • Emotional difficulties Respondents highlighted that: • High blood Phe levels cause very serious symptoms and long-term effects on the brain. • The impact of blood Phe on the brain still largely unknown, but it is likely to be detrimental. • The brain damage experienced by people with PKU is not reversible or fully reversible.	Comments noted. The committee considered the responses to the ACD on this theme, and the comments made at the committee meeting. The risk of irreversible brain damage reduces with age, particularly after brain development is complete. So the adverse effects of being unable to follow the protein-restricted diet are considerably reduced in adults compared with the risks in childhood. Adults may still gain considerable benefit from sapropterin because of fewer symptoms related to raised phenylalanine levels, without having to follow the protein-restricted diet as strictly. However, these benefits are included in the economic modelling. Also, in adults the weight-based dose together with the higher average mg/kg dose results in costs that are considerably higher than in children, but the benefits are not correspondingly higher for adults. Even taking into account any uncaptured benefits in adults, the cost-effectiveness estimates are substantially higher than what NICE considers an acceptable use of NHS resources. So, it is not recommended for adults aged over 21. The guidance document has been updated. See sections 3.1, 3.2, 3.6, 3.13, 3.23, 3.29, 3.30, 3.34, 3.35, 3.36 and 3.38 of the FAD.
3) Impact of PKU and PKU diet on carers and family (61% of all 401 responses) **Children with PKU** Managing PKU and the PKU diet affects the entire family. Managing PKU and the PKU diet for children can have a substantial impact on parents': • Mental health • Quality of life. Respondents highlighted they experience a great deal of stress arising from managing their children's PKU symptoms, particularly mental health issues due to high Phe levels Parents of children with PKU constantly feel concerns, guilt, stress and or anxiety about: • Managing the PKU diet and getting their children to adhere to it, particularly the aspect of force-feeding children supplements. • Children's mental and physical health.	Comments noted. The committee considered the responses to the ACD on this theme and comments made at the committee meeting, and the guidance document has been updated. See sections 3.1, 3.5, 3.6, 3.7 and 3.23 of the FAD.

Stakeholder comment	NICE Response Please respond to each comment
• Increased Phe levels in children and their effects children's health. • What children are eating outside of home or parents' supervision. • Children being or feeling isolated socially or being bullied because of their PKU. • Brain damage that might occur because of high Phe levels or not getting the diet right. • Refusing children normal foods. • Explaining why their children cannot have normal foods. Parents of children with PKU often have to: • Work reduced / part-time hours or seek flexible working arrangements. • Completely stop working or change careers to care for their children. Respondents highlighted that managing the PKU diet can be a whole job in itself because of the additional time needed to: • Shop for appropriate foods, read and understand labels, plan meals several days in advance and cook PKU friendly dishes using Phe-free ingredients (which are notoriously difficult to cook compared to normal ingredients) • Measure and monitor the amount of food eaten and left over to calculate the right number of exchanges. • Liaise with GPs, pharmacies and dietitians to advocate for their children and ensure prescriptions are fulfilled appropriately, arrive on time or include items of food that are more palatable. • Organise care such as blood tests, appointments with GPs, dietitians and psychologists, and daily reminders for children to take medication and supplements. • Educate self and children on PKU, foods that are safe to eat, how to cook PKU friendly foods and manage the diet appropriately. • Educate or train relatives, teachers, school cooks or other carers looking after their children on PKU and the PKU diet, and the importance of measuring everything their children eat as well as ensuring they do not eat any foods that a 'forbidden'. • Plan any social gatherings such as birthday parties, meals out, play dates etc. or travelling abroad or domestically. The strain and stress of managing the PKU diet and dealing with symptoms resulting from high Phe levels can lead to arguments between family members, impact on relationships or even lead to break-ups and divorce. Siblings of children with PKU are also impacted by the condition and the PKU diet by: • Being deprived of normal activities such as meals out or eating normal foods as a family to protect to avoid isolating or making the child with PKU feel left out. • Receiving less attention from parents. Respondents reported that PKU and the PKU diet has a financial impact on the household income because of the reduction in working hours or career stops parents have to undertake to manage the diet and/or because of the additional costs incurred from buying prescription foods, trying to make the diet more varied or having to buy more expensive free-from foods.	
4) Adults with PKU Adults with PKU often require additional support from: • Relatives (parents, grandparents etc.) who help manage the PKU diet, either on a regular basis or when adults experience PKU symptoms due to high Phe. • Their partners who help manage the PKU diet (e.g., cooking, obtaining prescriptions, checking labels etc.) and provide support for dealing with PKU symptoms. • Their children who take on the role of carers and help with various aspects of the diet and PKU symptoms. Respondents indicated that they experience increased stress because of the PKU diet and PKU symptoms. PKU and the PKU diet impacts on families' ability to engage in social activities such as: • Eating out, because of the need for advance planning such as choosing as PKU-suitable restaurant and liaising with staff in advance to ensure they are equipped or willing to cater for an individual with PKU. • Travelling either domestically or internationally because of the high amount of prescription food needed to be packed.	Comments noted. The committee considered the responses to the ACD on this theme and the comments made at the committee meeting, and the guidance document has been updated. See sections 3.2, 3.5, 3.6, 3.7, 3.13, 3.23, 3.29, 3.32 of the FAD. The risk of irreversible brain damage reduces with age, particularly after brain development is complete. So the adverse effects of being unable to follow the protein-restricted diet are considerably reduced in adults compared with the risks in childhood. Adults may still gain

Stakeholder comment	NICE Response Please respond to each comment
Respondents indicated that PKU, its associated symptoms and the PKU diet have led to: • Adults with PKU still living with family or having to move back because they were unable to manage the diet or deal with PKU symptoms on their own. • Strained family relationships, family arguments, break-ups or divorce. • Adults with PKU having reduced time or being unable to spend time with their children.	considerable benefit from sapropterin because of fewer symptoms related to raised phenylalanine levels, without having to follow the protein-restricted diet as strictly. However, these benefits are included in the economic modelling. Also, in adults the weight-based dose together with the higher average mg/kg dose results in costs that are considerably higher than in children, but the benefits are not correspondingly higher for adults. Even taking into account any uncaptured benefits in adults, the cost-effectiveness estimates are substantially higher than what NICE considers an acceptable use of NHS resources. So, it is not recommended for adults aged over 21. The guidance document has been updated. See sections 3.1, 3.2, 3.6, 3.13, 3.23, 3.29, 3.30, 3.34, 3.35, 3.36 and 3.38 of the FAD.
5) Maternal PKU (59% of all 401 responses) Respondents disagreed with or expressed concerns about the decision to not recommend treatment with sapropterin for women with PKU. Respondents felt that NICE have not taken women experiences into account when making their decision. The PKU diet recommended for safe pregnancies is even more restrictive than what women are used to, with nearly 0 allowance for protein. Women's experiences and thoughts about pregnancy are mostly associated with despondency because of: • Anxiety around the strictness of pregnancy diet • Effect of stress of pregnancy on mental health • Additional stress of diet on top of pregnancy issues that can arise • Terrifying thoughts of high Phe effects on unborn child • Worry, stress and anxieties of unplanned pregnancy • Impact of pregnancy planning and success on romantic relationships and marriages • Need for considerations of abortions as option in case of maternal PKU syndrome or miscarriages • Discouragement from getting pregnant or instilment of fear of pregnancy by clinicians • Extreme guilt associated with high Phe effects on unborn child • Complexity and near impossibility of managing a job, the PKU diet and household or family duties • Inability to openly discuss pregnancy or ask for help Women with PKU are deterred from having children or even engaging in sexual activities or relationship because of the: • Fear, concerns or stress of high Phe effects on unborn child • Strict diet and low Phe levels needed for pregnancy • Extreme stress, guilt and/or shame of having a child with maternal PKU syndrome • Inability to maintain the ultra-low diet needed for pregnancy Women with PKU have difficulties achieving Phe levels suitable for pregnancy due to: • Severe illness • Nausea or sickness due to pregnancy	Comments noted. The committee considered responses to the ACD on this theme and comments made at the committee meeting, and the guidance document has been updated. Sapropterin is recommended as an option for treating hyperphenylalaninaemia that responds to sapropterin in people with phenylketonuria (PKU), only if they are pregnant (from a positive pregnancy test until birth). See section 1.1 of the FAD. See also sections 3.3, 3.6, 3.19, 3.20, 3.24, 3.31, 3.37 of the FAD.

Stakeholder comment	NICE Response Please respond to each comment
• Complexity or strictness of PKU diet • Hormone changes • Prior suboptimal Phe control • Mental health • Unpalatable supplements • Exhaustion • Eating disorders due to PKU diet • Learning disabilities The effects of maternal PKU syndrome on the unborn child are severe and can include: • Disability • Cardiac effects such as congenital heart disease • Microcephaly • Intellectual disability • Brain damage / neurological issues • Intrauterine growth • Brain damage / harm occurs in first 6 weeks of pregnancy • Delayed learning • Delayed development • Spontaneous abortion / miscarriage • Low birth weight • Congenital defects • ADHD • Autism spectrum disorder Respondents suggested that sapropterin should be available for: • All women of childbearing age • Women who are trying to conceive • Women who are pregnant • After pregnancy Respondents indicated that treatment with sapropterin during and after pregnancy could: • Allow for better coping with PKU diet • Reduce the risk of high Phe levels to the unborn child • Help maintain low Phe levels • Reduce anxiety, stress and concerns around the effect of high Phe levels on the unborn child • Improve mood, reduce depression and enable women to better care for their newborn child	
6) Discriminatory draft guidance (55% of all 401 responses) Respondents felt that NICE had not considered treating people fairly and highlighted that the draft guidance was discriminatory on the basis of: • Age • Disability • Pregnancy or maternity • Sex • Ethnicity	Comments noted. The committee was aware that age-based recommendations must be objectively justified, and they should be avoided when possible. It considered the justification in this case is the need to secure acceptable cost efficacy in the interests of the NHS as a whole. Age itself is both an indicator of potentially greater benefit, coupled with lower cost of treatment. The reason for the cost-

Stakeholder comment	NICE Response Please respond to each comment
• Race Respondents also indicated that treatment with sapropterin should be available to all people with PKU who respond to it.	effectiveness estimates being higher in the over 18 population are explained in this guidance, as are the reasons for having 22 as the age for stopping treatment. The committee explored alternative approaches but could not find any better alternative to this approach. See sections 3.32 and 3.36 of the FAD. NICE is aware that a recommendation for use during pregnancy is necessarily only of benefit to people who become pregnant. This is permitted by s.17(6)(a) of the Equality Act 2010. See section 3.37 of the FAD.
7) Living experience of adults with PKU (53% of all 401 responses) Respondents indicated that PKU and the PKU diet have a substantial effect on adults' ability to: • Manage work or staying in work • Engage in daily activities or day to day life • Maintain adequate mental health • Development of anxiety • Socialise or communicate clearly with peers, colleagues, friends and family • Manage or finishing studies • Advance in their careers of choice • Maintain or adhere to the PKU diet • Avoid obesity, eating disorders or gastrointestinal issues • Avoid depression, suicidal ideation or self-harm • Develop and maintain personal and romantic relationships • Live independently or manage a household • Maintain adequate quality of life • Maintain adequate blood Phe control • Maintain family relationships • Avoid stress • Maintain physical health • Travel abroad or domestically or eat out with friends, family and peers • Having to explain PKU and the PKU to friends, co-workers, restaurant servers to be accommodated • Engage with clinical services or be able to advocate for themselves • Return to diet • Adjust their mood • Live a normal life • Get adequate nutrition from food Adults with PKU are disadvantaged by the condition and may struggle to maintain PKU diet because of: • Learning disabilities or difficulties • Cognitive impairments	Comments noted. The committee considered the responses to the ACD on this theme, and comments made at the committee meeting, and the guidance document has been updated. See sections 3.2, 3.5, 3.6 of the FAD.

Stakeholder comment	NICE Response Please respond to each comment
• Lower IQ scores • Neurological changes Adults with PKU frequently experience the following symptoms: • Low mood / mood swings / irritability / anger • Anxiety • Poor concentration or inability to focus • Brain fog • Depression • Fatigue, exhaustion, tiredness or lethargy • Memory loss • Headaches or migraines • Tremors • Paranoia and/or agitation • Shakes • Pain • Low bone density • Low motivation Respondents highlighted that adults with PKU have additional needs in the form of: • Psychological support and/or therapy • Support from family, carers, friends and/or work colleagues • Counselling • Mental health support • Education on PKU diet	
8) Missing costs from cost-effectiveness model (43% of all 401 responses) Respondents indicated that the following health care system costs, which have not been included in the cost-effectiveness model, are substantial and should be considered: • Cost of any medications for PKU comorbidities such as anti-depressants, ADHD medications etc. • Cost of medical care of comorbidities, particularly psychiatric, psychology or counselling costs • Costs of maternal PKU and care for children with maternal PKU syndrome • Costs of additional specialist care for PKU and diet side effects • Increased dietetic and health professional costs for poor metabolic control or nutritional deficiency • Speech therapy for babies with maternal PKU syndrome • Costs of care for patients with learning disabilities • Costs of dietary non-adherence of people with learning disabilities • Costs of nursing time for people with PKU in care homes • Dental costs • Costs of surgeries such as gallbladder removal, gastrotomy Respondents highlighted that community costs should also be included in the cost-effectiveness model such as: • Costs of GP or nurse visits • Cost of social services involvement for children with poor Phe control, early help or social care for children with maternal PKU syndrome • Costs of additional education and support in schools and university • Costs of extra educational needs for children with maternal PKU syndrome.	Comments noted. The committee considered the responses to the ACD on this theme and comments made at the committee meeting, and the guidance document has been updated. See sections 3.13, 3.23, 3.24 of the FAD.

Stakeholder comment	NICE Response Please respond to each comment
Respondents indicated that patient and societal costs are also likely to be substantial and include: • Loss of earnings through time spent managing the diet • Loss of earnings through time spent caring for children with maternal PKU syndrome • Costs of Disability Living Allowance, Personal Independence Payments or Disabled Student Allowance • Loss of work productivity due to reductions in hours or stopping work altogether • Reduced tax payments	
9) Experience of PKU diet (42% of all 401 responses) The PKU diet is not like a normal diet and can lead to the development of side effects such as: • Gastric or digestive issues • Disordered eating • Teeth issues such as tooth decay • Weight fluctuations • Nausea or vomiting • Mouth ulcers • Alopecia • Stunted growth • Pain • Irregular periods PKU diet alone does not prevent high Phe levels, which can occur because of illness, menstruation, stress, lack of eating or exercise. Patients were advised to come off the PKU diet according to past clinical practice and are struggling to return or adhere to the PKU diet as a result. Respondents felt that NICE had ignored the quality of life benefits of diet reduction for adults. Respondents indicated that the PKU diet is difficult to maintain, adhere to and even adjust to because of: • Its time-consuming nature involving buying products from different shops to maintain variety, read and understand labels, cook with difficult ingredients, liaise with GPs and pharmacies to get the right prescription foods and in the correct amounts. • Unpalatable and badly smelling supplements • Acidic or bitter supplements • Few healthy or normal foods allowed in the diet • Increased costs to have variety of foods in the diet • Need to weigh and record all foods eaten • Constant feeling of hunger or satiety • Need to take monthly blood tests and organise prescriptions and shopping trips for PKU-friendly foods • The high-carbohydrate and sugar content of PKU foods and supplements • Inefficient absorption of synthetic amino acid supplements compared to natural amino acids. Respondents highlighted people with PKU struggle to maintain PKU diet or adhere to it consistently because of: • High Phe levels and PKU symptoms • Coming off diet in the past (on their own or due to clinician advice) • Cognitive impairments or disability • Complexity and strictness of diet • Few normal foods available • Expensive free-from foods and supplements • Lack of or reduced support from family, carers or health professionals • Delayed access to or difficulty obtaining prescription foods	Comments noted. The committee considered the responses to the ACD on this theme and comments made during the committee meeting, and the guidance document has been updated. See sections 3.1, 3.2, 3.4, 3.5, 3.6, 3.17, 3.23 of the FAD.

Stakeholder comment	NICE Response Please respond to each comment
• Full-time or shift work • Indisposition towards supplements or food neophobia • Lack of or limited access to kitchens, cooking equipment and/or prescription food storage space Respondents indicated that the side effects of the PKU diet and the stress of having to constantly adhere to it can have an impact on: • Social interactions and socialising with friends, peers and family • Feeling isolated, left out or bullied or leading to self-isolation as a coping mechanism • Mental health • Academic performance • Physical health • Cognitive function • Ability to sleep • Concentration • Emotional capacity	
10) Dose limit at 10 mg/kg (24% of all 401 responses) Respondents questioned the dose limit or indicated that it should not be imposed. Respondents felt that: • The dose of sapropterin should be based on individual needs and that the 20 mg/kg dose should be available to those who benefit from it. • Doctors should have flexibility in prescribing sapropterin between 5 and 20 mg/kg according to the summary of product characteristics. • Restricting the dose to 10 mg/kg would lead to the exclusion of children who are responsive to higher doses. • The dose limit will reduce the effectiveness of sapropterin Some respondents highlighted need for clarity on how the dose will be administered in practice. Some respondents indicated that from personal experience an increase in dose to 20 mg/kg can have a dramatic effect on symptoms and diet relaxation.	Comments noted. The committee considered the responses to the ACD on this theme and comments made during the committee meeting, and the guidance document has been updated. The dose for children can be increased above the starting dose of 10 mg/kg, only if target blood phenylalanine levels are not achieved at a dose of 10 mg/kg. So, it is recommended for treating PKU in people under 18, normally at a dose of 10 mg/kg. See sections 1.1, 3.11, 3.21, 3.28, 3.30 of the FAD.
11) Comorbidities (13% of all 401 responses) Respondents indicated that people with PKU have additional comorbidities, which can make management of the PKU diet more difficult or affect quality of life: • Effect on managing PKU diet o Depression o Anxiety o Learning disability o Gastrointestinal disorders o ADHD o Osteoporosis / osteoarthritis o Autism o Psychiatric conditions o Parkinson's disease o Dementia o Intracranial hypertension o Down's syndrome	Comments noted. The committee considered the responses to the ACD on this theme and comments made during the committee meeting, and the guidance document has been updated to include some of the more common comorbidities. See sections 3.2, 3.5, 3.6, 3.23 of the FAD.

Stakeholder comment	NICE Response Please respond to each comment
o Deafness • Effect on quality of life o Diabetes / obesity o COPD / asthma o Polycystic ovaries o Bulimia o Body dysmorphia o Anorexia o Endometriosis o Epilepsy o Fibromyalgia o Liver issues o Alopecia o Dermatillomania (excoriating disorder) o Skin disease o Subarachnoid brain haemorrhage o Squashed pituitary gland o Kidney issues o Psoriatic arthritis Some respondents also highlighted that people with PKU can have comorbidities resulting from high Phe levels: • Dyslexia • Spastic paraparesis • Peripheral nephropathy • Demyelination	
12) Sapropterin patent expiry and future generics (2% of all 401 responses) Respondents indicated that the patent exclusivity for sapropterin has expired and that generics are currently being produced, which are likely to be cheaper and therefore more cost-effective than Kuvan.	Comments noted. The committee considered the responses to the ACD on this theme and comments made during the committee meeting, and the guidance document has been updated. See section 3.38 of the FAD.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
Individual stakeholder and expert comments on ACD			
1	[BioMarin International Limited]	In regard to the recommendation of sapropterin limited only to phenylketonuria (PKU) patients that are under 18 years of age, BioMarin (the Company) would like to state that all PKU patients, responding to treatment, could benefit from the sapropterin treatment. The health economic model that the company provided, indicates that for patients, below 18 years old, who start treatment and remain for lifetime, sapropterin is a cost-effective treatment in comparison to the standard of care when considering NICE's cost effectiveness thresholds. This finding is further confirmed in the new decision tree model that was submitted to the committee. The Company believes that this should be the correct interpretation of the data carried through into the policy.	Comments noted. The committee considered the responses to the ACD on this theme and the comments made at the committee meeting. The risk of irreversible brain damage reduces with age, particularly after brain development is complete. So the adverse effects of being unable to follow the protein-restricted diet are considerably reduced in adults compared with the risks in childhood. Adults may still gain considerable benefit from sapropterin because of fewer symptoms related to raised phenylalanine levels, without having to follow the

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			protein-restricted diet as strictly. However, these benefits are included in the economic modelling. Also, in adults the weight-based dose together with the higher average mg/kg dose results in costs that are considerably higher than in children, but the benefits are not correspondingly higher for adults. Even taking into account any uncaptured benefits in adults, the cost-effectiveness estimates are substantially higher than what NICE considers an acceptable use of NHS resources. So, it is not recommended for adults aged over 21. See sections 3.1, 3.2, 3.6, 3.13, 3.23, 3.29, 3.30, 3.34, 3.35, 3.36 and 3.38 of the FAD.
2	[BioMarin International Limited]	In page 3, the appraisal consultation document states that *"there is no clinical trial or registry evidence to show whether sapropterin reduces the need for a protein-restricted diet or how it affects quality of life"*. The Company would like to state again that there are numerous publications showing that sapropterin treatment contributes to the decrease of the use of protein supplements. A list of relevant references follows in support to the Company's argument: *[References received but not reproduced in this table]* Furthermore, the long-term PKU registries, KAMPER in Europe and PKUDOS in the US, also shows that patients receiving sapropterin experience decrease in their blood phenylalanine (Phe) levels while their natural protein intake increases. The above data has been corroborated by a panel of UK clinical experts that supported a minimum of 50% reduction in the use of protein supplements, potentially reaching 100% in highly responsive patients.	Comments noted. Wording amended in the 'Why the committee made these recommendations section', to state **"**There is no clinical trial or registry evidence to show *how much* sapropterin reduces the need for a protein-restricted diet, or how it affects quality of life *or brain development*"
3	[BioMarin International Limited]	In page 4, the ACD states that "the dose of sapropterin is based on weight", the Company would like to clarify that it is the total daily dose that is based on weight. The dose per kg for a patient will not be affected if their weight is higher, all patients would remain on the same dose, i.e. 10 mg/kg regardless if they weight 20 or 70 kgs. It is the total daily dose that would increase.	Comments noted. Wording amended in the 'Why the committee made these recommendations section' of the FAD.
4	[BioMarin International Limited]	In pages 4 and 21, the ACD states that "there is not enough evidence on how sapropterin might be used to prevent harm to the unborn child in women with PKU who are pregnant or trying to conceive" and "avoiding harm to the developing foetus was clearly important, and the committee welcomes comments and further evidence on the potential use of sapropterin in women with PKU of childbearing age, or those planning pregnancy, to prevent harm to the unborn child", respectively. The Company would like to clarify that the number of maternal PKU patients, if they are to be included in the policy, will be small. UK clinical experts estimate that there are approximately 50 to	Comments noted. The committee considered these responses and comments made at the committee meeting, and the guidance document has been updated. Sapropterin is recommended as an option for treating hyperphenylalaninaemia that responds to sapropterin in people with phenylketonuria (PKU), only if they are pregnant (from a positive pregnancy test until birth). See section 1.1 of the FAD. See also sections 3.3, 3.6, 3.19, 3.20, 3.24, 3.31, 3.37 of the

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		60 PKU pregnancies per annum in the whole of UK. Of these pregnancies, it is estimated that the number of pregnant patients who will be in clinic and responsive is approximately 10 per annum. These patients might also require sapropterin treatment only for 6 to 9 months. The UK clinical experts have also confirmed that Phe tolerance increases as the foetus grows and starts to metabolise Phe itself which enables mothers to take more natural protein. In comparison to the life-time costs that would be associated with managing a child with PKU Syndrome, offering the option of sapropterin to pregnant PKU patients would result in negligible overall budget impact. Furthermore, the Company would like to provide further evidence to confirm that sapropterin is associated with the same benefits in terms of reduction in blood Phe levels and increased dietary Phe intake in the maternal PKU population as in the overall PKU population. PKUMOMS, the PKU in the Maternal Phenylketonuria Observational Program is a sub- registry of PKUDOS with two data cuts, in June 2013 and December 2018. The June 2013 data-cut of the PKU-MOMS sub-registry contained data from 21 pregnancies in women with PKU, five of whom were treated with sapropterin before pregnancy (but not during pregnancy), and 16 of whom were treated with sapropterin during pregnancy. Excluding data for spontaneous abortions (n = 4), the data show that the mean of the median blood Phe levels (204.7, SD: 126.6 µmol/L; n = 14) for women treated with sapropterin during pregnancy was 23% lower and had a 58% smaller standard deviation compared with the blood Phe (267.4, SD: 300.7 µmol/L; n = 3) for women who were not treated with sapropterin during pregnancy (i.e. treated prior to pregnancy group). Women on sapropterin during pregnancy experienced fewer blood Phe values above 360 µmol/L. When median blood Phe concentration was < 360 µmol/L throughout pregnancy, 75% (12/16) of pregnancy outcomes were normal versus 40% (2/5) of pregnancy outcomes when the median blood Phe was > 360 µmol/L. Grange et al. 2014, publication from PKU-MOMS, clearly shows that sapropterin during pregnancy leads to better Phe control. (Grange 2013) The December 2018 data-cut of the PKU-MOMS sub-registry included data from ** women reporting ** pregnancies (several patients remained in the study throughout multiple pregnancies) with a mean sapropterin exposure during pregnancy of [redacted] ([redacted]) (BioMarin, data on file). The mean sapropterin dose was [redacted] mg/kg/day prior to pregnancy ([redacted]), [redacted] mg/kg/day during pregnancy ([redacted]), and [redacted] mg/kg/day after pregnancy ([redacted]). Mean blood Phe was [redacted] µmol/L ([redacted]) prior to pregnancy, [redacted] µmol/L ([redacted]) during the 1st trimester, [redacted] µmol/L ([redacted]) during the 2nd trimester, and [redacted] µmol/L ([redacted]) during the 3rd trimester. The following birth outcome data were available for the December 2018 data-cut (reported as adverse event data): • Of [redacted] pregnancies which ended in spontaneous abortion, [redacted] had at least one episode of maternal blood Phe > 360 µmol/L recorded during pregnancy. [redacted]Of [redacted] pregnancies with birth outcome data available, [redacted] were reported as normal and [redacted] were reported as abnormal. [redacted]	FAD.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		[redacted] At the January 2017 data-cut of KAMPER, [redacted] women participated in the KAMPER maternal sub-registry, with a total of [redacted] pregnancies being reported ([redacted]). Of the [redacted] pregnancies with available data, all [redacted] resulted in full term live birth deliveries, with all infant conditions at birth reported as normal. At the January 2019 data-cut of KAMPER, data from [redacted] were available. The mean age at delivery was [redacted] ([redacted]) years. The sapropterin dose was constant prior to, during, and after pregnancy, with a median dose of [redacted] mg/kg/day; the mean duration of exposure during pregnancy was [redacted] days ([redacted]). Maternal blood Phe concentrations were either within the clinical range ([redacted]) or high ([redacted]) during the 1st trimester of pregnancy, were within the clinical range (n = [redacted]) during the 2nd trimester, and were either within the clinical range (n = [redacted]) or low (< 120 µmol/L, n = [redacted]) during the 3rd trimester. Furthermore, additional publications including, Feillet 2014 and Nyuzuki 2019 further state that sapropterin use in pregnant woman leads to better blood Phe control and increased Phe tolerance. Feillet 2014 also reported the offspring of the seven pregnancies were all normal babies with normal birth measurements and outcomes. Nyuzuki 2019 reported normal growth and development of the child confirming the efficacy and safety of sapropterin in maternal PKU. International best practice guideline (Muntau 2019), also recommends sapropterin response testing for pregnant woman with PKU.	
5	[BioMarin International Limited]	In page 5, the ACD states that “childhood is the most critical period for brain development”. The Company would like to state that brain development continues up to the age of 25 (which is also stated in page 6 of the consultation document), thus adolescence and early adulthood are also critical periods for brain development, education and social development. Furthermore, it has been widely demonstrated that adolescence and early adulthood are periods when Phe control becomes problematic.	Comments noted. The FAD has been updated, see section 3.2 of the FAD.
6	[BioMarin International Limited]	In page 6, the ACD states that “Clinical experts estimated that 10% to 20% of patients struggle to maintain control of blood Phe levels”. The Company would like to present data from Walter 2002 publication which show that adherence to a Phe-restricted diet is extremely challenging with as many as 75% of adolescents being unable to keep their blood Phe levels within the recommended target range. (Walter 2002) A similar observation from the US shows that Phe levels increase as age increases. This assessment of current management by Jurecki et al. included PKU clinics across the US in 2015 covering approximately 50% of PKU patients followed in clinics in the US showed that 12% of patients aged 0-4 years old had Phe levels higher than 360 µmol/L, 29% of patients aged 5-12 years old had Phe levels higher than 360 µmol/L and 40% of patients aged 13-17 years old had Phe levels higher than 360 µmol/L.	Comments noted. Section 3.2 of the FAD has been amended to state “…many adults with PKU find it difficult to maintain good control of blood Phe levels.”

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
7	[BioMarin International Limited]	In page 6, the ACD states that "good control of blood Phe levels (below 200 micromols per litre) should be maintained if possible, but there are no strict guidelines or target Phe levels used in clinical practice". However, it is clearly stated in the 2017 EU Guidelines that pregnant PKU patients should maintain their Phe levels between 120 to 360 micromol/L (van Spronsen 2017) and UK clinical experts follow the European PKU guidelines.	Comments noted. Section 3.3 of the FAD has been amended.
8	[BioMarin International Limited]	In pages 17 and 18, the ACD states that "the model time horizon is not long enough to capture long-term brain damage in people with PKU and the model is not appropriate to capture the effects of PKU in pregnancy". The Company would like to state that owing to the teratogenic effects on children born to mothers with PKU, the model included an additional utility gain of [redacted] that sapropterin can potentially bring. This was presented to the Committee in the new decision tree model.	Comments noted. Section 3.19 of the FAD refers to the company's additional utility gain as a proxy for anxiety in pregnant women.
9	[BioMarin International Limited]	In page 19, the ACD states that "the ERG advised that the utility reductions may be double counted, because the reductions were already captured for different PKU symptom states". The Company would like to clarify that utility reductions have not been double counted. The health state vignettes that were presented to the general population in Sweden and clinical experts in England, did not include a description for intellectual disability and IQ deficits, hence inclusion of these in the decision tree model is not double counting.	Comments noted. Section 3.16 of the FAD has been changed to note the ERG's concerns.
10	[BioMarin International Limited]	In page 19, the ACD states that "the ERG did acknowledge that increased blood Phe levels can harm the unborn child, but the extent of lost utility is unclear, as is the effect of sapropterin on that utility loss". The Company will like to recount 2 publications, Lenke et al. 1980 and Koch et al. 2003. High Phe concentration in PKU mothers crosses the placenta by active transport, resulting in 70% to 80% increased foetal concentration of Phe compared with maternal concentration. Elevated Phe is toxic and teratogenic to a developing foetus. Women of child-bearing age with high Phe during and before pregnancy leads to an increased risk of spontaneous miscarriage (24%), intrauterine growth retardation (40%), microcephaly (73%), global developmental delays (92%), and congenital heart defects (12%) in their offspring. These risk of teratogenic effects in offspring, can be potentially reduced by sapropterin use pre-conception and during pregnancy [Feillet 2014 and Nyuzuki 2019]. The decision tree model used an increase in utility of [redacted] to address this reduced long-term risk of abnormalities to the child.	Comments noted. The committee considered these responses and comments made at the committee meeting, and the guidance document has been updated. Sapropterin is recommended as an option for treating hyperphenylalaninaemia that responds to sapropterin in people with phenylketonuria (PKU), only if they are pregnant (from a positive pregnancy test until birth). See section 1.1 of the FAD. See also sections 3.3, 3.6, 3.19, 3.20, 3.24, 3.31, 3.37 of the FAD.
11	[BioMarin International Limited]	In page 21, the ACD states that "the committee concluded that escalation above the dose of 10 mg/kg for children and 12.5 mg/kg for adults would have a significant effect on the cost effectiveness of the treatment". The Company will like to state that in the ERG model that was presented to the committee, dose escalation from 10 mg/kg to 12.7 mg/kg had limited impact. The results are presented in the table below: *[Table of results received but not reproduced in this table]* Furthermore, the new decision tree model submitted by the Company to the committee, the ICERs were:	Comments noted. The company agreed with NICE that the figures they submitted in response to the ACD on this issue were incorrect.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		[Table of results received but not reproduced in this table] Thus, the dose increase to 12.7 mg/kg has shown limited impact on ICER for <18-year olds.	
12	Royal College of Physicians (RCP)	At the RCP we have had three separate responses to this appraisal consultation document. These are from the British inherited Metabolic Disease Society (BIMDG) and from two RCP Fellows: an RCP recognised expert Dr Robin Lachmann who treats a significant number of these patients and from [redacted] who cares for patients with neurodegenerative disease in older age and is a parent of a child with phenylketonuria (PKU). The RCP endorses the view of the BIMDG but in addition would like to add the following points: We have serious concerns about stopping sapropterin treatment at the age of 18 and recommend that this is changed. The decision to recommend stopping sapropterin treatment at the age of 18 seems arbitrary and will coincide with a particularly vulnerable period in these young people's lives. We are very concerned that stopping Kuvan at the age of 18 will result in significant numbers of young adults with PKU discontinuing diet. This transition period is already known to represents the highest risk time for reduced compliance and becoming lost to treatment, for people with PKU. There is some evidence that raised phenylalanine (Phe) may have a wider impact than just on brain development with higher rates of depression and a wide range of other medical conditions. We understand the need for cost effectiveness but note there is some evidence that suboptimal dietary adherence is associated with poorer quality of life scores. To ensure optimum outcomes by treating young people until neurodevelopment is completing, then we recommend treating until at least the age of 25.	Comments noted. The committee considered these responses and comments made during the committee meeting, and the guidance document has been updated. See section 1.1 of the FAD. The committee recognised that stopping treatment and relying on diet alone at 18 years old is not ideal. It would benefit young adults if treatment with sapropterin could be continued for as long as possible during final brain development and transition into adulthood. The maximum age at which sapropterin can be considered a cost-effective use of NHS resources is 21. However, for this to be cost effective people would need to continue the dose they were having when they were under 18. In practice this may mean that some young adults may need more dietary control alongside sapropterin between the ages of 18 and 21 than they would with a higher dose. See sections 3.6, 3.30, 3.34, 3.36 and 3.38 of the FAD.
13	Royal College of Physicians (RCP)	We have serious concerns that Sapropterin is not being offered as a first line treatment to women with PKU. There is a great deal of evidence concerning the teratogenic effects of Phe and the need for women with PKU to obtain strict metabolic control throughout pregnancy. There should be no question of the cost-effectiveness of sapropterin in this setting. Women with PKU who are planning pregnancy, and the healthcare professionals looking after them need access to every means possible of maintaining phenylalanine levels within the target range for pregnancy. On Page 7 of the consultation the committee concluded that high blood Phe levels in pregnancy can have harmful effects on the unborn child. Early control of Phe levels, ideally before conception, would reduce the risks. Data indicate clearly that use of Sapropterin in pregnancy is safe and prevents the maternal PKU syndrome. Consideration should also be given in the vulnerable period post-partum while mothers are	Comments noted. The committee considered these responses and comments made at the committee meeting, and the guidance document has been updated. Sapropterin is recommended as an option for treating hyperphenylalaninaemia that responds to sapropterin in people with phenylketonuria (PKU), only if they are pregnant (from a positive pregnancy test until birth). See section 1.1 of the FAD and sections 3.3, 3.6, 3.19, 3.20, 3.24, 3.31, 3.37 of the FAD.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		adjusting to caring for their children and managing a tightly restrictive diet is virtually impossible. We suggest that all women of child-bearing age (14-45 years) are assessed for Sapropterin responsiveness – and those who are responsive to be offered Sapropterin as a first-line option when they are actively planning pregnancy (the pre-conception period) and for the duration of pregnancy and for a short period postpartum.	
14	Royal College of Physicians (RCP)	NICE has not given any recommendations on how Sapropterin-responsiveness should be determined longer-term. We have concerns about the lack of clear criteria concerning sapropterin responsiveness and the lack of definition of what constitutes a satisfactory response to treatment. One of the major issues in using sapropterin to treat PKU is that it has different effects in different patients. It is important to precisely define which patients are to be considered responsive to sapropterin. This involves describing the method of testing as well as what constitutes an adequate response in terms of lowering Phe and/or increasing natural protein intake. Sapropterin is used as an adjunct to diet. Dietary treatment on its own can be used to achieve target phenylalanine levels in all patients, although this can be very challenging. Therefore, for different patients the goals of adding sapropterin to dietary treatment are different. For some, the goal will be to reduce Phe levels into the normal range whilst for the majority, the goal will be to allow patients to maintain target phenylalanine levels with less dietary restriction. Because of this it is also very important to define criteria for what constitutes a satisfactory long-term response to sapropterin. Without clearly defined definitions of responsiveness and response, it will be very difficult to translate any NICE recommendations into clinical practice. The final recommendations need to address these issues in detail. This has previously been done by a policy working group convened by NHSE and the committee might find it very useful to look at the NHSE policy proposal the 'Interim Clinical Commissioning Policy: Sapropterin for phenylketonuria (All ages)'. Although many patients in the UK are not currently genotyped, data regarding the determination of Sapropterin-responsiveness by *PAH* genotype is also increasing (see http://www.biopku.org/home/biopku.asp).	Comments noted. This committee considered this outside the remit of this appraisal as response is defined in the summary of product characteristics. See section 3.28 of the FAD.
15	Royal College of Physicians (RCP)	We would request that the review date of the policy is reduced from 3 to 2 years to enable new evidence to be considered as further research becomes available. We are aware that several studies are near publication.	Comments noted. Section 5.1 unchanged. The standard review date is 3 years, however stakeholders can request an earlier review if any new evidence becomes available before then.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
16	I am a patient expert nominated by the National Society for Phenylketonuria	I strongly disagree with the idea that Sapropterin be used as a treatment option for hyperphenylalaninemia in responders only up until the age of 18, for the following reasons: • The recommendation to stop treatment at the age of 18 is reckless and undermines The European Guidelines for the Treatment of PKU that stipulates the need for treatment for life. • The draft recommendation also neglects the whole adult PKU population that are responsive to Sapropterin. • No justification has been provided by the committee as to why the age of 18 has been selected to cease Sapropterin. Neuroimaging research demonstrates that brain development continues beyond the age of 18. For example, the frontal lobes, home to key components of the neural circuitry underlying "executive functions", are the last areas of the brain to mature and may not be fully developed until halfway through the third decade of life (Sowell et al 92). Indeed, the draft accepts that, *"adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25."* • In normal circumstances the transition period to adulthood is a continuous process of rapid developmental change that starts accelerating at age 16, and for most, is completed by age 30. During this period, most individuals take steps to live more independently and depend less on family support. These steps, which involve completing school and training, launching work lives, and developing relationships with others, can greatly influence much of their future adult life. The World Health Organization (2020) recognises adolescence as one of the most rapid stages of human development and a phase in which biological maturity precedes psychological maturity, noting that the changes taking place during adolescence can have health consequences over the course of a person's life. Therefore, the idea to withdraw a treatment option that would lead to a serious lifestyle change at the age of 18 could drastically interrupt this important developmental period and is therefore unethical. • No guidance has been provided as to how treatment would be stopped, and how services would provide provision for the re-introduction of the ultra-harsh low protein diet. • The cost of these additional services has not been factored into NICE's cost analysis. Children's clinics are often equipped with kitchens to teach the children to cook PKU recipes and demonstrate new products. Most adult PKU clinics are an add-on to another department and don't have the necessary facilities for dietary therapy training. Neither child or adult services normally have dedicated mental health teams and due to the extra load on the mental burden of transition, therefore would be essential to see a requirement of psychological care being added. • NICE does not appear to have taken into account just how greatly Sapropterin liberates the dietary choices a person with PKU can make. It is not going to be easy for a person to switch from eating 40 grams of natural protein to 10 grams of natural protein overnight. • A person's ability to select food and to make decisions about how much to eat is affected by memory for specific eating episodes (episodic memory). Thus, NICE cannot expect a person that has previously been treated with Sapropterin to select low protein foods with	Comments noted. The committee considered these responses and comments made during the committee meeting, and the guidance document has been updated. See section 1.1 of the FAD The committee recognised that stopping treatment and relying on diet alone at 18 years old is not ideal. It would benefit young adults if treatment with sapropterin could be continued for as long as possible during final brain development and transition into adulthood. The maximum age at which sapropterin can be considered a cost-effective use of NHS resources is 21. However, for this to be cost effective people would need to continue the dose they were having when they were under 18. In practice this may mean that some young adults may need more dietary control alongside sapropterin between the ages of 18 and 21 than they would with a higher dose. See sections 3.6, 3.30, 3.34, 3.36 and 3.38 of the FAD.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		ease and without giving thought to the cognitive processes that underpin food selection. • NICE appears to have a simplistic view or indeed has not regarded how eating behaviours are shaped. A child that has learnt what foods they can eat whilst being treated with Kuvan will not simply be able to unlearn those food choices. Habitual behaviour related to food choices is guided by information about immediate consequences (such as taste, likeability and familiarity) and it is not sensitive to representations of delayed outcomes, (such as the knowledge that eating 2 biscuits would not fall within the day's protein restriction). Habits (so, for example the routine of living with PKU with Sapropterin treatment) are performed automatically and non-consciously and going against the grain of habit (life without Sapropterin and having to learn new dietary habits) is difficult, requiring sustained effort (executive cognitive control, bearing in mind high phe levels reduces cognitive control) to monitor and abandon existing habits, and to acquire new ones. • Healthy eating (choosing low protein foods) relies on impulse control; therefore, a person with PKU in order to make the right food choices needs to have the ability to inhibit their impulses. Deficits in 'inhibitory control' are often found in people with treated PKU. • It appears that NICE's recommendation to terminate treatment at aged 18 is because the ERG cost model did not incorporate the benefit of preventing long-term brain damage after the age of 18. Why this was not factored in does not make sense especially when one reads the discussion of clinical considerations accepts that long term brain damage has the potential to occur after the age of 18. Therefore, NICE's decision is discriminatory as the difference in treatment between age groups has not been properly considered or justified. *[References received but not reproduced in this table]*	
17	I am a patient expert nominated by the National Society for Phenylketonuria	*"There is no clinical trial or registry evidence to show whether Sapropterin reduces the need for a protein-restricted diet or how it affects quality of life".* This is a contentious statement as presently there is no standardised PKU specific instrument via which the true extent of quality of life can be measured/captured in the UK. • Generic instruments are problematic as they lose specificity for the PKU health condition. Also, one has to remember cross-cultural comparability; different countries and cultures may have tested quality of life in patients with PKU and not found improvements in quality of life after using Sapropterin, but that does not mean that the same results would be found in the UK. • Also the committee needs to consider the challenges in assessing quality of life in patients with PKU. For example, PKU is a dynamic condition, and as such it is dependent upon Phe control and therefore neurocognitive function will be variable. Issues with neurocognitive function will affect a person's self-awareness. Many adult patients with PKU have reduced executive function because of high Phe levels and are therefore not as able to assess their own quality of life or put into words their experience (Waisbren, 2010). • It is challenging to collect information on health-related quality of life in adults with PKU.	Comments noted. Wording amended in the 'Why the committee made these recommendations section', to state **"**There is no clinical trial or registry evidence to show *how much* sapropterin reduces the need for a protein-restricted diet, or how it affects quality of life *or brain development*" Section 3.15 of the FAD accepts that quality of life was not assessed in sapropterin studies because of difficulties in measuring it in people with PKU and committee noted that the TTO study is the best available source of utility values for PKU symptom states and, although not necessarily robust, it is the only available evidence.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		People with PKU can have cognitive problems, self-reflecting and describing their condition. For example, some patients with low IQ and executive dysfunction/communication skills could be unaware, fail to understand or are unable to articulate why they need alternatives to dietary treatment. Indeed, it has been found that some patients are only able to report improvement in functioning and have insight about their deficits after receiving treatment to control their blood Phe, (Simon, 2008). • Another reason why a person wouldn't necessarily talk about having a reduced QOL is because, they may not consider that they do so. For example, my son would not be able to affectively put into words how dramatically his life has been negatively impacted by not having control of PKU. One reason he wouldn't talk about having a reduced QOL is because everything that he does in his daily life is about managing all of what he struggles with, consequently and subsequently he manages me to meet all of his needs. He is happy in not going out, he does not need to go to the shops, he does not need to go to work, because he has me. • There is a lack of research when it comes to PKU and the caregivers lived experienced. The management of PKU places a significant burden on carers; there's the gravity of initial diagnosis and the administering of the diet, and it is acknowledged that patients with PKU can suffer from behavioural, mood, emotional, and social problems, psychiatric disorders, intellectual development delays, and neurological deficits. • There is no break from a Phe restricted diet and Sapropterin would help in finding a break. Leaving a patient with PKU for a length of time is not something that carers routinely do due to worries that the patient will not receive the correct foods or that they would be given a forbidden food or that someone else would not adequately manage the diet (i.e. log, weigh and calculate all foods). *[Reference received but not reproduced in this table]*	
18	I am a patient expert nominated by the National Society for Phenylketonuria	Statements of brain damage - Long term brain damage in adults - NICE has said: "...adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25." NICE has also said "and there is no risk of long-term brain damage in adults". • Neuroimaging research demonstrates that brain development continues beyond the age of 18. For example, the frontal lobes, home to key components of the neural circuitry underlying "executive functions", are the last areas of the brain to mature and may not be fully developed until halfway through the third decade of life (Sowell et al 92). Indeed, the draft accepts that, *"adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25."* • Adulthood may represent an additionally vulnerable time for PKU individuals, as the compensational mechanisms for Phe accumulation may be reduced by the normal brain aging processes. Correspondingly, reports provide evidence that some adult PKU patients may develop intellectual disability and mild parkinsonian signs. • Thomas recruited young adults with PKU (average age 27.5) and older adults without	Comments noted. Section 3.2 of the FAD address the issue of long-term brain damage in adults. The committee recognised that stopping treatment and relying on diet alone at 18 years old is not ideal. It would benefit young adults if treatment with sapropterin could be continued for as long as possible during final brain development and transition into adulthood. The maximum age at which sapropterin can be considered a cost-effective use of NHS resources is 21. However, for this to be cost effective people would need to continue the dose they were having when they were under 18. In practice this may mean that some young adults may need more dietary control alongside sapropterin between the ages of 18 and 21 than they would with a higher dose. See sections 3.6, 3.30, 3.34, 3.36 and 3.38 of the FAD.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		PKU (average age 69.2). In both groups, speed of processing was slow and both groups were impaired in their complex executive function (to a similar level) too. Given that the normal ageing brain declines in the aforementioned areas, Thomas concluded that speed of processing and executive function is at risk of declining even further in adults with PKU as they reach older age (a decline that is more than what is seen in normal ageing). Thus, if adults were able to continue restricting their Phe intake the decline in processing speed and executive function could be mitigated, (L Thomas at the ESPKU conference in 2020), Sapropterin would help this. • Piloto et al (2019) evaluated cerebrospinal fluid (CSF) neurotransmitter levels in adults with PKU and age-matched controls. In PKU patients, CSF Phe concentrations were closely related to plasma levels, which were four to six times higher than in in controls. The study demonstrates that serotonin and dopamine metabolites are reduced in adult PKU patients and correlate with specific grey matter atrophy patterns. These findings place a focus on serotonin metabolism in the pathophysiology of PKU and may support a more rigorous Phe control, especially in older patients, to prevent. These findings firmly support the idea of treatment for life to prevent early brain damage through aging. • Some adults have low IQ due to poor phenylalanine control in childhood – therefore neurological damage is permanent. There is much evidence to suggest that the inability to sustain good metabolic control in childhood is associated with a decline in IQ score and executive function and will have a negative influence in adulthood (Jahja et al. 2017; Koch et al. 2002; Waisbren et al. 1980). • Waisbren et al, (2007) found that each increase of 100 µmol/l in lifetime Phe for early-treated PKU patients was associated with a 1.9–4.1 reduction in IQ. • Jaha et al 2017 showed that high blood phenylalanine levels in childhood, affect adult cognitive flexibility, executive motor control, executive function in daily life and adult mental health. • Weglage (2013) also showed that high blood phenylalanine levels in childhood and adolescence were related to poorer IQ, information processing and attention in adulthood. *[References received but not reproduced in this table]*	The risk of irreversible brain damage reduces with age, particularly after brain development is complete. So the adverse effects of being unable to follow the protein-restricted diet are considerably reduced in adults compared with the risks in childhood. Adults may still gain considerable benefit from sapropterin because of fewer symptoms related to raised phenylalanine levels, without having to follow the protein-restricted diet as strictly. However, these benefits are included in the economic modelling. Also, in adults the weight-based dose together with the higher average mg/kg dose results in costs that are considerably higher than in children, but the benefits are not correspondingly higher for adults. Even taking into account any uncaptured benefits in adults, the cost-effectiveness estimates are substantially higher than what NICE considers an acceptable use of NHS resources. So, it is not recommended for adults aged over 21. See sections 3.1, 3.2, 3.6, 3.13, 3.23, 3.29, 3.30, 3.34, 3.35, 3.36 and 3.38 of the FAD.
19	I am a patient expert nominated by the National Society for Phenylketonuria	This statement needs revision "*Children with PKU frequently experience difficulty with focus, depression or anxiety, disordered eating, digestive problems, headaches, low mood and sadness, feeling tired all the time and being in a heightened emotional state (including aggressiveness, psychosis and paranoia) because of high Phe levels."* Thus it was concluded, *"that there is a need for a treatment that can reduce PKU symptoms and give people with PKU and their carers peace of mind about blood Phe levels".* • The above statement is not limited to children, adults have the same experiences too. Adults with PKU and carers of adults with PKU equally need peace of mind about Phe levels.	Comments noted. Section 3.6 of the FAD has been amended.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
20	I am a patient expert nominated by the National Society for Phenylketonuria	The description of the condition in paragraph 3.1 is incomplete, ignoring the high prevalence of comorbidities which are described at paragraph 2.2.3 of the ERG report. Many patients also have very distorted relationships with food due to the nature of the PKU diet. Losing weight will have an impact on metabolic control; it causes Phe to increase. In addition to this, the supplements (and perhaps the quantities of fruit) whilst being freely available can cause reflux and gastric problems. • People with PKU live with a range of comorbid conditions; disordered eating is a huge problem faced by many living with PKU. The high prevalence of disordered eating patterns has been accepted in the European Guidelines. Page 29, *"living with a lifelong severe dietary restriction may adversely affect eating attitudes and behaviours and increase susceptibility to the development of eating disturbances".* • Below is just one example of a person trying to manage life with PKU whilst also living with other health challenges. *[Case study A received but not reproduced in this table]*	Comments noted. The committee considered these responses and comments made during the committee meeting, and the guidance document has been updated to include some of the more common comorbidities. See sections 3.2, 3.5, 3.6, 3.23 of the FAD.
21	I am a patient expert nominated by the National Society for Phenylketonuria	The statement at paragraph 3.5 does not adequately describe that many adult patients are dependent on others to help them manage either their dietary treatment or the impairments they have as a result of PKU. - NICE has not taken into account the effect that PKU has on family members that help manage PKU symptoms or PKU treatments. • Adults that do manage the dietary treatment usually only do so because of the support they receive from parents and or partners. • In the patient expert report I submitted, I clearly wrote about the care I provide for my adult children; one needing constant mental health support, whilst the other is in need of support to manage the diet. Many adults are in the same position as my daughter; her ability to adequately manage the PKU diet is compromised as she is not left with enough hours to do all of her prescription orders, shopping and cooking. Not being able to have a full-time job places serious economic disadvantages upon people in the same position as my daughter.	Comments noted. Section 3.6 of the FAD has been updated to include responses received on this issue.
22	I am a patient expert nominated by the National Society for Phenylketonuria	*"NICE concludes that it was not possible to recommend KUVAN in any group of adults due to the cost effectiveness estimates in adults".* NICE has failed to consider the great wealth of evidence in relation to maternal PKU and the benefit to children born to a PKU mother. This treatment is not fair or just. Women of childbearing age should be given the treatment of Kuvan for the following reasons: • The rate of unplanned pregnancy for women with PKU is the same as the general population. Women with PKU have the right to have sex and the right to have their reproductive rights supported in a non-discriminatory way. • Many women with PKU are petrified of becoming pregnant (whether planned or not) in case their Phe levels would be damaging to the unborn child, *[Reference received but not reproduced in this table]*	Comments noted. The committee considered these responses and comments made at the committee meeting, and the guidance document has been updated. Sapropterin is recommended as an option for treating hyperphenylalaninaemia that responds to sapropterin in people with phenylketonuria (PKU), only if they are pregnant (from a positive pregnancy test until birth). See section 1.1 of the FAD. See also sections 3.3, 3.6, 3.19, 3.20, 3.24, 3.31, 3.37 of the FAD.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		Below is a real and typical example of how women in the UK feel about pregnancy. *[Case study B received but not reproduced in this table]* *[Case study C received but not reproduced in this table]* *[Reference received but not reproduced in this table]*	
23	I am a patient expert nominated by the National Society for Phenylketonuria	*"The committee concluded that high blood Phe levels in pregnancy can have harmful effects on the unborn child. Early control of Phe levels, ideally before conception, would reduce the risks"*. But then went on to contradict themselves with the statement that there is "*not enough evidence on how Sapropterin might be used to prevent harm to the unborn child in women with PKU who are pregnant and trying to conceive*". To not recommend the use of Sapropterin to all women of childbearing age is reprehensible. • Maternal phenylketonuria (MPKU) is a well-recognized complication of PKU and one of the most potent teratogenic syndromes of pregnancy. • The fetal brain and heart are particularly vulnerable to high maternal concentrations of phenylalanine. The levels of phenylalanine in fetal blood are higher than would be expected based on the maternal blood levels because phenylalanine crosses the placenta by an active transport process. Children born to women who have PAH deficiency on unrestricted diets have a 92% risk of developmental delays, a 73% risk of microcephaly, and a 12% risk of congenital heart defects as well as growth delay and seizures • Control of maternal blood phenylalanine during pregnancy prevents most if not all of these complications.	Comments noted. The committee considered these responses and comments made at the committee meeting, and the guidance document has been updated. Sapropterin is recommended as an option for treating hyperphenylalaninaemia that responds to sapropterin in people with phenylketonuria (PKU), only if they are pregnant (from a positive pregnancy test until birth). See section 1.1 of the FAD. See also sections 3.3, 3.6, 3.19, 3.20, 3.24, 3.31, 3.37 of the FAD.
24	I am a patient expert nominated by the National Society for Phenylketonuria	NICE has not included the costs of preventing neurological damage to the children of women with uncontrolled PKU (ERG report, section 5.5) in their costs calculations. Below are two real examples taken from the community. *[Case study D received but not reproduced in this table]* *[Case study E received but not reproduced in this table]* *[References received but not reproduced in this table]*	Comments noted. The committee considered these responses and comments made at the committee meeting, and the guidance document has been updated. Sapropterin is recommended as an option for treating hyperphenylalaninaemia that responds to sapropterin in people with phenylketonuria (PKU), only if they are pregnant (from a positive pregnancy test until birth). See section 1.1 of the FAD. See also sections 3.3, 3.6, 3.19, 3.20, 3.24, 3.31, 3.37 of the FAD.
25	I am a patient expert nominated by the National Society for	The committee states that adults with high Phe suffer from, "*impaired executive function, reduced autonomy, impaired social maturity, difficulty forming relationships and neuropsychiatric symptoms such as depression, anxiety and inattention*". How then, does the committee recommend that people suffering from the aforementioned problems lower their Phe without the help of Kuvan?	Comments noted. The committee considered the responses to the ACD on this theme and the comments made at the committee meeting and the guidance document has been updated.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
	Phenylketonuria	• The burden of treatment is felt more greatly when people suffer with co-morbidities such as depression, anxiety and inattention. Some adults cannot deal with the complexity of their special diet and are unable to properly deal with the diet in the long term, consequently their wellbeing is compromised. • High blood phenylalanine levels are related to poorer IQ, information processing and attention in adulthood. Lower IQ lessens the patient's ability to manage a low phenylalanine diet. Low IQ is linked with social disadvantage (low paid job, living in poverty), which in turn lessens the ability to apply the stringent dietary treatment, (Weglage, 2013). • Overall, non-adherent patients report more emotional issues related to PKU (Borghi et al 2020). Patients receiving BH4 report lower practical and emotional impacts because of lower burden of care associated with the diet (Bosch et al 2015). *[References received but not reproduced in this table]*	The risk of irreversible brain damage reduces with age, particularly after brain development is complete. So the adverse effects of being unable to follow the protein-restricted diet are considerably reduced in adults compared with the risks in childhood. Adults may still gain considerable benefit from sapropterin because of fewer symptoms related to raised phenylalanine levels, without having to follow the protein-restricted diet as strictly. However, these benefits are included in the economic modelling. Also, in adults the weight-based dose together with the higher average mg/kg dose results in costs that are considerably higher than in children, but the benefits are not correspondingly higher for adults. Even taking into account any uncaptured benefits in adults, the cost-effectiveness estimates are substantially higher than what NICE considers an acceptable use of NHS resources. So, it is not recommended for adults aged over 21. See sections 3.1, 3.2, 3.6, 3.13, 3.23, 3.29, 3.30, 3.34, 3.35, 3.36 and 3.38 of the FAD.
26	I am a patient expert nominated by the National Society for Phenylketonuria	.*"Clinical experts estimated that 10% to 20% of patients struggle to maintain control of blood Phe levels".* This statement grossly underestimates the true figure of people struggling with their Phe level • The NHS England Commissioning Policy states "*Up to 28% of pre-school children do not attain recommended Phe targets; this figure rises to 79% of teenagers and 88% of adults (Enns et al., 2010)."* • Ford et al in 2018 reported the experiences of over 300 adults with PKU, many described their dietary management as complex and impractical and so abandoned treatment, with some withdrawing from medical. *[References received but not reproduced in this table]*	Comments noted. Section 3.5 of the FAD has been amended, with the figure of 10-20% removed.
27	I am nominated by the National Society for Phenylketonuria	The recommendation that sapropterin should be used until the age of 18 and then stopped is inappropriate and dangerous. The reasons are set out below: • The guidance accepts that there is a risk of permanent harm to the brain in young people after the age of 18. There is no clinical basis for the proposed stopping criteria at aged 18. The draft guidance also accepts there is a risk of neurological problems from high phe, including brain fog, executive functioning deficits, anxiety and depression. • Children that have grown up using sapropterin do not develop the eating behaviours of children with PKU. In the survey NSPKU undertook of children taking sapropterin, parents	Comments noted. The committee considered these responses and comments made during the committee meeting, and the guidance document has been updated. See section 1.1 of the FAD The committee recognised that stopping treatment and relying on diet alone at 18 years old is not ideal. It would benefit young adults if treatment with sapropterin could be continued for as long as possible during final brain development and transition into adulthood. The maximum age at which sapropterin can be considered a cost-effective use of

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		described children that enjoyed normal foods – fish and chips, shepherd's pie, yogurt, pizzas and ordinary bread. These foods are forbidden to children were taking sapropterin. Young people with PKU are trained from being weaned to deny themselves foods and to learn the routines and thought processes of the PKU diet. This is a drastic modification of ordinary eating behaviours that requires inculcation from an early age by parents and their metabolic dietitian. Families start trying to teach children they have a "special tummy" from being toddlers. This process continues through different stages of childhood and adolescence, as at each stage the child and the family needs to navigate how they live with a diet that is radically different from "normal". Children raised using sapropterin will have had a radically easier diet and childhood but they will also be less equipped at aged 18 to manage a PKU diet. Therefore the draft guidance will lead to young people who start adulthood without the coping skills and eating behaviours required to control their phenylalanine levels by a strict PKU diet. • NSPKU held community online meetings to discuss the draft guidance attended by about 130 people. Families and individuals expressed concern that the draft guidance indicated that Committee did not understand the realities of living with PKU. It was said that the PKU diet is very hard, requiring families to have to encourage children to accept prescribed low phenylalanine foods and deny themselves foods they might want to eat. Making a switch at 18 would be difficult/impossible. A teenager – aged 15, said he wasn't sure if he would start taking sapropterin as stopping would be so hard. He thought the guidance was wrong. Adults with PKU said – often drawing from their own experiences - that young people at 18 were very vulnerable as they are trying to start an independent life, studying or starting work. An adult with PKU who had taken sapropterin on a clinical trial and then stopped as a young woman thought that withdrawing sapropterin at 18 would cause people to have severe mental health problems. Many people or families have confided in me about mental health breakdowns occurring at this age linked to the struggle to manage PKU dietary therapy independently. • The Committee did not perform any enquiry into whether into the risks of withdrawing sapropterin for young people aged 18. There is no evidence that suggests that individuals can reliably return to the PKU diet once they have stopped. In fact there is evidence that returning to the PKU diet is rarely successful. Young people who have been raised on the PKU diet will not be "returning" to a strict PKU diet, they are being asked to commence something they have never before experienced. Evidence from the general population is that eating behaviours are formed in childhood and modification is difficult. There is no evidence for the assumption that young people, at aged 18, will reliably be able to control their phenylalanine levels by diet. • The Committee did not consider the impact of the recommendation that sapropterin be withdrawn aged 18 on service provision. Transition from paediatric to adult clinics typically occurs at 18 or close to this age. Transition services for children with PKU are not robust with some areas lacking fully developed adult services. It is very common for young people to experience a failure to manage their PKU at this life stage with impacts	NHS resources is 21. However, for this to be cost effective people would need to continue the dose they were having when they were under 18. In practice this may mean that some young adults may need more dietary control alongside sapropterin between the ages of 18 and 21 than they would with a higher dose. See sections 3.6, 3.30, 3.34, 3.36 and 3.38 of the FAD.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		on their mental health and education. At least in theory, transition should be a gradual process whereby the young person learns the skills to manage their own care as an adult at a time which is developmentally appropriate for them as an individual. The withdrawal of sapropterin would involve a young person having therapy withdrawn at a developmentally inappropriate time – and needing significant input to attempt to learn to manage PKU via strict diet therapy for the first time. Those resources do not exist. • I am able to comment on this issue from my own experience. My son commenced sapropterin treatment on a clinical trial aged 5 which led to him to start eating foods which were once considered "dangerous". These dangerous habits include eating bread, which his metabolic consultant told me I should never let him acquire a taste for! I was told when he was young to avoid giving any ordinary bread to him as then he would realise it tastes nicer than PKU bread. In this early training from the hospital I was told it was safer to completely avoid foods which could lead him into trouble later on. When he started taking Kuvan he inevitably started eating foods which I never thought he ever would. He does not remember eating prescription foods and has grown up with eating and social habits which without sapropterin would lead him to have spiralling phenylalanine levels. He is "sensitive" to high phe which affects his mood and functioning. Withdrawing treatment would risk very poor outcomes for him. It is these considerations which led BioMarin to confirm that supplies would continue for him and the other clinical triallists after the trial ended, as recorded in the BMJ https://www.bmj.com/content/365/bmj.l1874 This was a relief, but I am very concerned about the proposed stopping criteria because I can see the risk that lies ahead. • Any consideration of the risks of withdrawing treatment needs to consider the position of young women with PKU who are likely to becoming sexually active at around age 18, when sapropterin therapy will be withdrawn under the proposed guidance. If they are unable to manage their phe levels via diet poor outcomes from pregnancy is a risk. The European Guidelines recommend robust transition planning for young women to mitigate this risk; by definition an abrupt withdrawal of sapropterin treatment will increase risk of young women and their children having children affected by Maternal PKU. • NICE's decision to withdraw treatment at aged 18 is based on the ERG cost model which did not include the benefit of preventing long-term brain damage after the age of 18. This is not logical when the discussion of clinical considerations accepts that long term brain damage can occur after the age of 18. There are also other failings in the costs modelling for adults. In conclusion NICE's decision is discriminatory as the difference in treatment between age groups has not been properly considered or justified.	Sapropterin is recommended as an option for treating hyperphenylalaninaemia that responds to sapropterin in people with phenylketonuria (PKU), only if they are pregnant (from a positive pregnancy test until birth). See section 1.1 of the FAD. See also sections 3.3, 3.6, 3.19, 3.20, 3.24, 3.31, 3.37 of the FAD.
28	I am nominated by the National Society for Phenylketonuria	The statements on the risks of long term brain damage in adults are inconsistent and lack robust evidence or investigation. "*Clinical experts explained that brain development peaks at around age 12. After this high Phe levels are unlikely to affect IQ. However, adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25. In adults, high Phe concentrations can result in short-term symptoms, which are considered reversible by lowering Phe levels through diet.*" Thereafter this statement is	Comments noted. The committee considered the responses to the ACD on this theme and the comments made at the committee meeting, and has updated the guidance document. The risk of irreversible brain damage reduces with age,

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		inappropriately simplified further to "*there is no risk of irreversible brain damage in adults with PKU*". • This statement is not accepted but it is manifestly illogical that the same guidance goes on to conclude "*there is no risk of irreversible brain damage in adults with PKU*". By definition "adults" includes people aged 18-25. The statement on the brain developing until "around 25" is vague. • The statement about the risk of irreversible brain damage in adults is inaccurate and oversimplifies (to the point of inaccuracy) statements from Technical Engagement. NICE is under a duty to ensure that the appraisal reflects consensus views on PKU treatment and the overall breadth of professional clinical opinion. I am not aware of any published peer reviewed paper that makes a statement to the effect that there is no risk of irreversible brain damage in adults with PKU. • The draft guidance includes a statement from me as patient expert that there are adult patients with "severe symptoms and irreversible brain damage" but this seems to have been dismissed as incorrect. However the literature includes independent descriptions which corroborate this evidence. The European Guidelines state "*Some adults who have not been treated early and continuously have been reported to develop leukoencephalopathy, spastic paraparesis, brisk reflexes, tremor, Parkinsonism, psychiatric symptoms and vision loss*". There is no statement in the literature which states that there is "no risk of irreversible brain damage" in adults – instead there are more tentative statements that <u>some</u> problems can be improved or even reversed. • Similarly, NHS England developed a policy proposition through the Sapropterin Working Group which included a broad committee with metabolic consultants and dietitians. This recommended treatment for children and adults, noting the occurrence of florid neurological abnormalities manifesting in adulthood such as spasticity of the legs and visual loss. • The PKU community is concerned by broad statements about the safety of high phenylalanine levels. In our community many adults live with impairments sustained by high phenylalanine levels when their dietary treatment was stopped in childhood – on the recommendation of metabolic consultants - who said their "brain had sealed" or "stopped developing". Where there is such a difficult history of incorrect advice about high phenylalanine levels ceasing to be a danger the patient community would like to see a cautious and evidence based approach. It is patients and their families who bear the risk. The life span of early treated patients with PKU is still not complete. • Knowledge of the development of the brain has developed in the past decades and continues to develop. NICE needs to ensure that its guidance is based on robust evidence and a cautious approach to uncertainty. It is submitted that the broad statement	particularly after brain development is complete. So the adverse effects of being unable to follow the protein-restricted diet are considerably reduced in adults compared with the risks in childhood. Adults may still gain considerable benefit from sapropterin because of fewer symptoms related to raised phenylalanine levels, without having to follow the protein-restricted diet as strictly. However, these benefits are included in the economic modelling. Also, in adults the weight-based dose together with the higher average mg/kg dose results in costs that are considerably higher than in children, but the benefits are not correspondingly higher for adults. Even taking into account any uncaptured benefits in adults, the cost-effectiveness estimates are substantially higher than what NICE considers an acceptable use of NHS resources. So, it is not recommended for adults aged over 21. See sections 3.1, 3.2, 3.6, 3.13, 3.23, 3.29, 3.30, 3.34, 3.35, 3.36 and 3.38 of the FAD.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		- that there is no evidence that irreversible brain damage can occur after the age of 25 - is unsound and should be withdrawn. • Professor Shawn Christ was asked to comment on the draft NICE guidance by a member of the PKU community. Shawn Christ, Ph.D. is Associate Professor, Dept of Psychological Sciences, MRI Director, Cognitive Neuroscience Systems (CNS) Core Research Facility, University of Missouri-Columbia. Dr Christ responded by email on 18 March 2021, which was copied to me. He stated "*In glancing through the Appraisal Consultation Document and Committee Papers Document, I was alarmed by the repeated assertion within the texts that "There is no risk of irreversible brain damage in adults with PKU." **In my professional opinion, there is insufficient evidence to make this claim**. The literature supports the notion that phe-related brain damage incurred in adults with PKU is more reversible than brain damage incurred in children – but this does not mean that the brain damage in adults is fully reversible. For example, a number of studies (e.g., Cleary et al, 1995 in JPeds; Clocksin et al, 2021 in MGM) have found improved white matter integrity following phe level reduction in adults. Importantly, however, even after improvement, the white matter integrity in the PKU patients in these studies continued to be compromised relatively to healthy non-PKU individuals. There is a fair amount of research from our lab and others suggesting that higher phe levels in adults are associated with increased risk of neurological, cognitive, and psychological problems. The extent to which these effects are reversible is definitely still an open question. In my opinion, the conclusion that they are completely reversible (as implied in the aforementioned documents) is quite premature and not necessarily supported by the PKU literature or our general understanding of how risk factors such as this work.*" • A recent paper provides a review of neurological cases which presented in adulthood *[Reference received but not reproduced in this table]*. This reviewed 8 new cases of neurological manifestations in adults with PKU with 22 cases reported in literature. These were adults – mostly early diagnosed and treated who presented with debilitating neurological symptoms such as the inability to walk and visual loss. MRI scans showed white matter lesions in the brain. The review showed that reinstituting treatment to lower phenylalanine levels could improve symptoms. However the review does not support the statement that the adults' problems were all reversible. The cases studies generally show partial improvements, some adults still had brain lesions, sight loss, tremor and other neurological symptoms. The damage was improved with treatment but not reversed. • The review also notes the presence of white matter lesions in patients with phe levels above 600, who are presently considered to be asymptomatic. The paper noted that it is suspected that such lesions are involved in early neurodegenerative disease. • In my role as a patient advocate I see adults who develop neurocognitive symptoms in adulthood or whose daily functioning declines. These are problems that manifest in adulthood and shows evidence of progression. In the course of patient advocacy work, I am aware that many patients have MRI scans showing PKU related damage to the brain.	

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		• Further, the emphasis on irreversible neurological harms and reversible harms can mask the unfortunate truth; which is that many patients who have problems like forgetfulness and executive functioning problems cannot sustain dietary treatment and hence are unable to "improve" their symptoms. This was stressed in the NHS England policy which noted that "In adults, neurocognitive and executive function deficits leads to inability to sustain dietary treatment, causing chronic poor blood phenylalanine control with negative impacts on mental health, quality of life, and daily functioning." This was a major factor in the reasoning to recommend sapropterin for all ages. • The draft guidance does not reflect the consensus of opinion about the issues experienced by adults with PKU with high phenylalanine levels. Currently, in the UK, a metabolic consultant at University Hospitals Birmingham NHS Foundation Trust is the principal investigator for an investigational gene therapy for adults with PKU. It seems unlikely that it would be ethical to conduct a clinical trial for an investigational gene therapy for adults with PKU unless there was a strongly held clinical view that the adults had significant ongoing unmet need. Similarly, Pegvaliase is a therapy developed and licensed for adults with PKU with high phenylalanine levels, which has been licensed by the EMA and FDA for adults only despite the possibility of very severe allergic reactions. By contrast, this draft guidance presents a picture that adults with PKU suffer very little risk from high phenylalanine levels. The email I have received from Professor Christ suggests that the statements in the draft guidance relating to the risk of high phenylalanine levels in adulthood are contentious and not evidence based. It seems likely that NICE has not accurately reflected the range of clinical views about the experiences of adults with PKU, perhaps due to the fact that it only consulted one professional working with adults with PKU . • In summary, the statement in the guidance about the risks of brain damage over the age of 18 are contradictory and unsound. It does not reflect the consensus of opinion on the disease in adults. There is a continuing risk of brain damage in adults with PKU. In addition many patients with symptoms are unable to sustain dietary treatment. • The draft guidance fails to accurately reflect the risks and experiences of adults with PKU. The approach to cost effectiveness is also unsound as it is based on omissions or flawed assumptions. Therefore the conclusion that the treatment is not cost effective in adults is unsound.	
29	I am nominated by the National Society for Phenylketonuria	This statement is inaccurate and should be removed/corrected: *"Clinical experts estimated that 10% to 20% of patients struggle to maintain control of blood Phe levels*". This is not consistent with published research or other recent consensus statements. This statement should be withdrawn. The NHS England Commissioning Policy states "*Up to 28% of pre-school children do not attain recommended Phe targets; this figure rises to 79% of teenagers and 88% of adults (Enns et al.,*	Comments noted. Section 3.5 of the FAD has been amended, with the figure of 10-20% removed.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		2010).”	
30	I am nominated by the National Society for Phenylketonuria	The draft guidance fails to reflect the prevalence of comorbidities linked to PKU, and their impact on patients and health resources are not accounted for in the ERG model. This means that the provisional recommendations are not a sound and suitable basis for guidance. • The description of the condition in paragraph 3.1 is incomplete, ignoring the high prevalence of comorbidities which are described at paragraph 2.2.3 of the ERG report. • From my experience with NSPKU I support the accuracy of the statement at 2.2.3 of the ERG report as I see these problems very frequently. The PKU diet allows sugar, fruit, some vegetables and fat freely. Normal calorie loss diets will be very challenging. Many patients also have very distorted relationships with food due to the nature of the PKU diet. Losing weight will have an impact on metabolic control; it causes phe to increase. In addition to this, the supplements (and perhaps the quantities of fruit) whilst being freely available can cause reflux and gastric problems. I know a patient with gastritis, obesity and diabetes who feels she cannot improve management of one of her conditions without impacting one of the others. • In my view, the ERG report and the draft guidance fails to reflect the high incidence of eating disorders within the PKU population. I know many patients who have been diagnosed with anorexia or have other diagnosed eating disorders. The PKU diet requires a very unnatural, vigilant relationship with food. • The co-morbidities are linked to significant impacts on quality of life, health and health resource use. These issues are relevant and should have been included in the QALY calculation for adult patients.	Comments noted. The committee considered these responses and comments made during the committee meeting, and the guidance document has been updated to include some of the more common comorbidities. See sections 3.2, 3.5, 3.6, 3.23 of the FAD.
31	I am nominated by the National Society for Phenylketonuria	The statement that there are “no strict guidelines or target Phe levels used in clinical practice” for women with PKU who are pregnant is not accurate. The NHS England Commissioning Policy adopted the European Guideline target phe levels for all patients (children, 12+/adults and pregnant women”. NICE guidance should be careful to accurately reflect clinical practice/opinion. The evidence review for the NHS England policy (performed by NICE) also referred to the European Guidelines target phe levels.	Comments noted. Section 3.3 of the FAD has been amended.
32	I am nominated by the National Society for Phenylketonuria	The statement that … “*the outcomes for pregnant women with PKU are better in the UK than in other countries such as the US*” is not evidence based and is not an appropriate statement for inclusion in the guidance in any event. • First the statement itself is not appropriate or clear. What does “other countries such as the US” mean? Countries without public health systems? High income countries? It is not clear why this statement might even have relevance as a measure of outcomes in this context.	Comments noted. Section 3.3 of the FAD has been amended.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		• Second, whilst there is some data showing poor outcomes in different countries, comparisons across different studies and countries are difficult as there is often different time-frames and different outcome measures. The statement does not have an evidence base to support it. • The NHS England Policy https://www.england.nhs.uk/wp-content/uploads/2013/04/e12-p-a.pdf includes detailed audit requirements. NHS England have confirmed (following a Freedom of Information request submitted by me) that no audit data was held or collected by them. There is no evidence that any outcome data was considered by NHS England in relation to the decision to not review the policy since 2013. • NHS England's continued failure to review this 8 year old policy - which is described as "not optimal" by the clinical experts – may be associated with poor outcomes for women and babies which could have been avoided. When was it realised it was not optimal and what is being done about it? In this overall context, it is offensive to include a statement which suggests that worse outcomes in other countries is a relevant factor to raise. • In conclusion, this statement lacks a reasonable evidential base, is unclear and lacks a reasonable purpose for inclusion.	
33	I am nominated by the National Society for Phenylketonuria	The description of the treatment pathway at 3.3 fails to address patients who cannot access the current treatment. As the treatment is self-managed and complex, many individuals cannot access any existing treatment. This is a hugely relevant issue explaining which adjunctive/alternative treatments are required.	Comments noted. The adverse effects of being unable to follow the protein-restricted diet are considerably reduced in adults compared with the risks in childhood. Even taking into account any uncaptured benefits in adults, the cost-effectiveness estimates are substantially higher than what NICE considers an acceptable use of NHS resources. See page 3 of the FAD in the 'Why the committee made these recommendations' section'
34	I am nominated by the National Society for Phenylketonuria	The statement at paragraph 3.4 that "Clinical experts noted that just over 50% of adults with PKU are on a protein restricted diet, while about 30% of adults have stopped their diet and the other 20% have difficulties maintaining it". • This statement lacks precision. First it is not clear that what is being measured are "adults with PKU" or "adults with PKU in clinic" or "early treated adults with PKU who have had contact with a clinic recently". The statement is not wholly consistent with the percentages given in paragraph 3.1 which say 10-20% of patients "struggle with control". • The different categories of patients are not clearly defined and it is not clear what the purpose of the categories are, either for describing patient's experience or for developing recommendations. In practice, for many patients, they may not be on diet because they can't cope with it. There may be a continuum of experience of struggling with maintaining their levels/ successfully maintaining their levels/ stopped trying to maintain their levels as they can't cope. Assigning people's experience to these categories is not so easy in	Comments noted. Section has been amended. Committee noted NHSE figures, and comments from clinical experts that around 50% of adults with PKU are on diet. See section 3.5 of the FAD.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		practice and the categories for many people aren't fixed – they might move between them for different reasons. For example a woman with PKU who experienced many severe PKU related symptoms told me she was able to control her levels because she had a new supportive partner who managed her treatment for her. Without the presence of her partner she had such severe executive functioning problems she couldn't cook safely on her own. Would you describe this situation as "having difficulties" with her diet, or just being "on diet"? As her experience is dependent on an unpaid carer, she is at risk of becoming "off diet" if the carer is no longer able or willing to assist her. The Committee should understand that these "categories" don't necessarily help describe unmet needs in adults with PKU. • The evidential basis for this statement is unclear. Only one adult clinician (London based) contributed to Technical Engagement. Patient cohorts may be different across England for various reasons (e.g. higher economic deprivation in some areas) and there was no mechanism within Technical Engagement to look for the impact of this.	
35	I am nominated by the National Society for Phenylketonuria	This statement needs revision "*Children with PKU frequently experience difficulty with focus, depression or anxiety, disordered eating, digestive problems, headaches, low mood and sadness, feeling tired all the time and being in a heightened emotional state (including aggressiveness, psychosis and paranoia) because of high Phe levels."* • All these statements are pertinent to adults with PKU and the guidance should be adjusted accordingly.	Comments noted. Section 3.6 of the FAD has been amended.
36	I am nominated by the National Society for Phenylketonuria	The statement at paragraph 3.5 does not adequately describe that many adult patients are dependent on others to help them manage either their dietary treatment or the impairments they have as a result of PKU. The patient expert reports submitted to NICE included a statement from a carer who described having to support her adult children with PKU; one of the young adults needed support with managing and maintaining her PKU treatment, and her son has mental health problems related to PKU. Other information about dependency on care in early treated PKU is ignored. Further, as should be apparent to the Committee, the adult patient cohort includes many people with high care needs, who have untreated or late diagnosed PKU. The European Guidelines on PKU note that "*untreated patients with severe intellectual disability and challenging behavioural problems have high support needs and some may live in social welfare homes*." This issue is discussed further below. Cognitive problems and learning disabilities are also prevalent amongst early treated people with PKU and this is also associated with care needs. The guidance fails to account for care needs or carer disutility associated with adults in its costs modelling and this is a significant failing.	Comments noted. Section 3.6 of the FAD has been updated to include responses received on this issue. The issues of costs of long-term brain damage, carers' costs, carer disutilities and comorbidities associated are discussed in section 3.23 of the FAD.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
37	I am nominated by the National Society for Phenylketonuria	The statement at paragraph 3.5 ignores the existence of people with undiagnosed/late diagnosed PKU with intellectual disability. This is a blind spot of the entire guidance; even the description of the patient population ignores a consideration of patients who are not attending clinics. A large proportion of people with untreated PKU or late treated PKU do not attend clinics. The issues with late treated/untreated PKU are discussed further below.	Comments noted. Section 3.6 of the FAD has been amended to include these issues.
38	I am nominated by the National Society for Phenylketonuria	The ACD does not adequately explore issues relating to people with learning disabilities. • First, I think it is helpful for the Committee to understand how learning disabilities might be present in the PKU cohort. These are – people with untreated PKU, people with late treated PKU, and people with early treated PKU who have PKU related cognitive impairments or other learning disorders. All these groups may not be attending metabolic clinics for care. People with learning disabilities are likely to be over-represented amongst lost to follow-up. Therefore the approach of the ACD - which is to look at who is attending clinics - is problematic from the start. • There is no patient registry, but there has been some work on trying to understand patient numbers with untreated PKU. The paper *'Adults with untreated phenylketonuria: out of sight, out of mind" Murphy, The British Journal of Psychiatry* (2008) details a survey to trace people with untreated PKU, estimate patient numbers and to understand their symptoms and behaviour. The discussion suggested that (as of 2008) there would be about 2000 people with untreated PKU in the population if their life expectancy was 65. • Jancar estimated a life expectancy of 57 *[Reference received but not reproduced in this table].* It is likely that patients with untreated PKU suffer the same decreased life expectancy due to inadequate NHS treatment for people with learning disabilities (NHS England Learning Disability Mortality Review (LeDeR) Program (https://www.england.nhs.uk/wp-content/uploads/2019/05/action-from-learning.pdf). It is not clear if PKU related factors also have an impact on life expectancy. It is reasonable to assume that there are significant numbers of patients with untreated PKU still alive who are not seen in metabolic clinics. It is my understanding that some patients with untreated PKU now do receive follow up care in metabolic clinics but this is unlikely to be comprehensive. • I am also informed that there are younger people with untreated/late treated PKU in the UK due to migration from countries without reliable new-born screening programmes at the time of their birth. • Murphy's paper surveyed the characteristics of individuals with untreated PKU who had been traced (n=79) and showed very high care needs for the patients with untreated PKU. The majority needed 24-h support, had behaviours that put their safety at risk and behaviours that put other's physical safety at risk. A significant proportion had epilepsy.	Comments noted. Section 3.6 of the FAD includes this issue. The risk of irreversible brain damage reduces with age, particularly after brain development is complete. So the adverse effects of being unable to follow the protein-restricted diet are considerably reduced in adults compared with the risks in childhood. Adults may still gain considerable benefit from sapropterin because of fewer symptoms related to raised phenylalanine levels, without having to follow the protein-restricted diet as strictly. However, these benefits are included in the economic modelling. Also, in adults the weight-based dose together with the higher average mg/kg dose results in costs that are considerably higher than in children, but the benefits are not correspondingly higher for adults. Even taking into account any uncaptured benefits in adults, the cost-effectiveness estimates are substantially higher than what NICE considers an acceptable use of NHS resources. So, it is not recommended for adults aged over 21. See sections 3.1, 3.2, 3.6, 3.13, 3.23, 3.29, 3.30, 3.34, 3.35, 3.36 and 3.38 of the FAD.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		• Brown and Guest, "*Economic impact of feeding a phenylalanine restricted diet to adults with previously untreated phenylketonuria" (Journal of Intellectual Disability Research*") details resource use associated with caring for people with untreated PKU. As of 1998, the mean annual cost for caring for an individual with untreated PKU was £83,996. It also noted the improvements in behaviour and quality of life that resulted from introducing a low phenylalanine diet. This reduced the care costs to £63,348. • The study concludes that the low phenylalanine diet leads to costs savings for the NHS in people with untreated PKU. However it does not include the costs associated with administering the PKU diet to people in care settings. The study also does not include any consideration of improvements to the life expectancy, health or quality of life of the individuals themselves. However it is clear that these would be substantial, as the patients were significantly less distressed and symptomatic. The European Guidelines also reports improvements such as improvement of motor function behaviour, less aggression, improved mood and sociability. It is also possible that patients would have better life expectancy. • Murphy's paper examined untreated PKU but we should also consider the population of people with late treated PKU, who will have been born between the invention of dietary therapy in the 1950s and new-born screening in 1969. Some patients in that era were diagnosed relatively swiftly through the earlier screening methods used prior to the Guthrie test, but some were diagnosed much later. This age group is also often affected by misguided medical practices from this era which believed that it was safe to withdraw dietary treatment from children. Within this group of late treated patients there can be wide disparities of outcomes, with some people with high support needs and some living independent lives. Many of patients were discharged from metabolic clinics decades ago. • It might be helpful to provide the Committee with examples of patients born in the 1950's and 60's. (1) One patient born in 1958, did not meet developmental milestones as a baby. After many tests and delays she was diagnosed with PKU. She was treated with PKU dietary treatment until she was about 4 years old, when her parents were told "her brain had sealed". She has never lived independently and now requires care. She has help and companionship from her father, who is now elderly, and a team of carers. She has never returned to a low phenylalanine diet. The family has had no contact from metabolic specialists since 1963. (2) Another patient known to NSPKU had PKU diagnosed in the first few months of life and was taken off PKU dietary treatment aged about 10. She now has many health problems and lives independently with a substantial care package and disability benefits. Her health problems became more significant as she aged. Carers visit several times per day. She has returned to a low phenylalanine diet which helps with her symptoms but the diet is administered by carers. (3) A man, born in the late 1960s and diagnosed via the "nappy test". Ceased dietary treatment in late teens. Now has executive functioning problems and short term memory problems that impact everyday activities. He returned to diet with the support of his clinic to improve his symptoms. His partner and mother supports him to maintain dietary treatment, for example by organising	

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		his meals and shopping and reminding him to have his supplements. He could not manage this without support as he struggles with organisation. • I am also aware of patients with early treated PKU who have learning disabilities or PKU related cognitive problems. These issues typically have an impact on whether the individual is able to manage the low phenylalanine diet independently. I am aware of people with PKU in the community who have problems like intense anxiety or problems with executive functioning which is a barrier to them being to getting a new referral to a metabolic clinic and turning up to the appointment. I am also aware of patients with PKU who are supported by informal family care. During the pandemic our helpline became aware of patients who significantly declined because this family care was no longer available – indicating that informal family care masks how many patients are reliant on care that would otherwise have to be publicly funded. I know patients awarded Personal Independence Payment benefits which indicates that the Department for Work and Pensions have assessed the individuals as needing help with daily living activities due to their disability. • The literature suggests there are barriers to the introduction of a protein restricted diet with patients with care needs. Many patients with untreated or late treated PKU have rigid behaviours and resist change. I am also aware that care arrangements themselves can be a barrier to a strict PKU diet. Hospitals frequently are unable to provide low phenylalanine diets. Care homes or domiciliary care will also have difficulties administering the diet; which are likely to be more problematic than for parental carers – e.g the high numbers of staff who may have responsibility for supervising the diet of an individual, reliance on external caterers, staff turnover, possibly (in some cases) a lack of motivation to handle a difficult task. • The behaviour and preferences of the individuals themselves may also be a barrier to reducing phenylalanine levels via dietary treatment. I am aware (though our helpline work) of an early treated adult patient who lacked mental capacity. She presented with neurological symptoms in adulthood and had high care needs. She expressed the wish to not return to dietary treatment. It was also noted that the in-patient settings under consideration for caring for her did not have the facilities to administer a low phenylalanine diet. In another case, I am aware of a patient who steals food within her care home environment as she is attracted to tasty foods. Our helpline is in contact with the carer of a late diagnosed patient who has very ingrained eating patterns; she has eaten the exactly the same meal for decades. • It is likely that sapropterin would have advantages for responsive individuals with untreated PKU or late treated PKU with care needs. Vernon (2010) records treating a 46 year old man with untreated PKU with severe mental retardation and behavioural problems. On sapropterin his phe levels reduced from 1255 lmol/L on an unrestricted diet to 308 lmol/L. Carers noted significant behaviorial improvements and indicated care needs lessened. The patient was able to have increased social interactions, and for the first time	

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		in his life was able to take a holiday with the other residents in his facility. • Vernon notes that there is low compliance with low phenylalanine diets in patients with untreated PKU and concludes that "*Our observation indicates that a trial of sapropterin is worthwhile even in severely affected PKU patients, and can have beneficial improvements on quality of life in this challenging population in whom dietary modifications may not be possible*." • Jaulent's paper of French case studies of adults presenting with severe neurological problems includes case studies of introducing either sapropterin or diet treatment alone to patients, who we can infer have care needs. Patient 1 was late diagnosed who presented with a disabling hand tremor. The patient was treated with sapropterin and diet leading to an improvement of symptoms and brain abnormalities. Patient 3 was early treated but had sub-optimal treatment in childhood and presented aged 37 with various symptoms including a walking disability. She was treated with sapropterin and diet which led to an improvement of neurological symptoms (with some issues still ongoing). The majority of the case studies state that patients found it hard to control their phenylalanine levels via the strict diet. *[Reference received but not reproduced in this table]* • I am not aware of any UK literature on treating adults with PKU with care needs with sapropterin, presumably due to the persistent lack of access to sapropterin treatment in this country. • It is likely that there will be significant QALY gains in patients with untreated PKU or late treated PKU with care needs who are able to take sapropterin. These calculations should take into account the significant costs of delivering the strict PKU diet in a social care setting. From my own experience, the dietary modifications required to treat a patient taking sapropterin can be relatively modest and suitable food choices are usually available from standard catering choices. For example, my son, who uses sapropterin, is able to eat hot school lunches from the standard choices the school offers. I believe this experience would indicate that the practical barriers to dietary treatment for patients with care needs could be overcome with sapropterin. There will not be the costs associated with training staff, preparing special foods or weighing phenylalanine portions and supervising food intake. The time associated with administering standard dietary treatment is 19 hours per week; I believe this would not be less for learning disabled adults with care needs. In my view, sapropterin would reduce the care costs associated with reducing phe levels for such patients. • I am also able to report on the experience of a family whose child has autism. It was difficult for him to adhere to the low phenylalanine diet as he didn't understand it. He had very strong preferences for high protein foods and an aversion to his protein supplement. The family were eventually able to access sapropterin via an individual funding arrangement. The drug allowed the child to manage his phenylalanine levels as the	

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		dietary modifications he required became much easier to manage. He could eat the foods he really loved without affecting his phe levels. As his levels improved, his behaviour also improved. • I therefore invite NICE to take into account that patients with learning disabilities, cognitive impairments and care needs form a significant section of the PKU community and that the ACD has failed to address this adequately. These patients may experience significant QALY gains from being able to use sapropterin, which will both improve their own health and reduce their care needs. The Committee should also take into account that many patients with care needs cannot access dietary treatment for the reasons discussed, and therefore the comparator is "no treatment". • The Committee should include a valuation of the cost of care delivered by family members which might otherwise have been provided by the NHS or personal social services as suggested by 5.5.13 of the Methods Guide. As I have attempted to explain, patients with learning disabilities or cognitive impairments typically cannot manage dietary treatment by themselves. Many adults rely upon others to help them adhere to dietary treatment or to manage the effects of high phenylalanine (e.g. tremors, forgetfulness). If informal family care is removed social services care is required to fill in the gaps. • Further, NICE needs to be mindful of the need to contextualise evidential gaps for this group of patients with a rare disease. This group has literally been "out of sight, out of mind" to research and the NHS. NICE cannot use an unreasonable approach to its evidential standards to perpetuate inequality for this group.	
39	I am nominated by the National Society for Phenylketonuria	The statement that there is "*not enough evidence on how sapropterin might be used to prevent harm to the unborn child in women with PKU who are pregnant and trying to conceive*" is wrong and is contradicted by statements within the guidance itself. The failure to make a recommendation to support women and their children was wrong. • In my work for the NSPKU I have been shocked by the unmet need in women with PKU and set out below some issues known to me. • A young woman with PKU previously took Kuvan on a clinical trial as a teenager and young adult. She had responded well. Access to the treatment was subsequently withdrawn. Many years later she became pregnant, on a carefully planned pregnancy with support from her metabolic team. She has always struggled with tolerating protein substitutes and in pregnancy this drastically worsened. She had hyperemeisis and amino acid supplements would trigger vomiting. She was hospitalised during her pregnancy to manage this but had dangerous phenylalanine levels. The stress of the situation was "nerve shredding" for the entire family. She was not offered access to sapropterin through the NHS England policy. She has stated her belief that women should be routinely offered sapropterin to help them through pregnancy.	Comments noted. The committee considered these responses and comments made at the committee meeting, and the guidance document has been updated. Sapropterin is recommended as an option for treating hyperphenylalaninaemia that responds to sapropterin in people with phenylketonuria (PKU), only if they are pregnant (from a positive pregnancy test until birth). See section 1.1 of the FAD. See also sections 3.3, 3.6, 3.19, 3.20, 3.24, 3.31, 3.37 of the FAD.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		• A lady planned a pregnancy with her metabolic team – this process is called "pre-con" by women with PKU and their dietitians. Getting her levels low enough was a huge struggle requiring support from her extended family and was very stressful. She did not conceive. This unsuccessful "pre-con" went on for a long time. She became convinced she would not conceive without fertility treatment and stopped her pre-con diet because it was so hard to maintain. She then conceived, naturally and completely unexpectedly with high phenylalanine levels. • Women with PKU can find the process of "pre-con" incredibly hard. The process of maintaining ultra low levels requires a huge effort. Women have to monitor the blood levels several times a week, requiring contact with their metabolic team. It must create immense pressure to conceive swiftly, but life is not always like this. There is a practice – recommended in the European Guidelines – to refer women to a fertility specialist early if they fail to conceive quickly. I am aware this happens in some clinics in the UK but not universally so. However this will not necessarily reduce the stress of the situation. • Many women may become pregnant without properly engaging on pre-con and present for metabolic care as swiftly as possible but the foetus will have been exposed to high phenylalanine levels at a crucial stage of pregnancy. Only half of PKU pregnancies follow the "textbook" plan for managing PKU in pregnancy. • Within the PKU community I am aware of girls and women who have had unplanned pregnancies which are either entirely concealed or the girl or young woman does not come forward for support until later in her pregnancy. NICE should consider the pressures that may surround young women with PKU. Sex and pregnancy may be stressful and they may feel shame and panic. They may also have issues related to their PKU which may make them vulnerable to an unplanned pregnancy which they then feel unable to confront. Women may have irregular periods or be using a contraceptive method where they do not expect to menstruate and are not aware of their pregnancy for some time. There is also evidence that women with a disability are more likely to experience sex against their will, engage in early sex and risky sexual behaviours, and these issues may be relevant here (*Holdsworth, Sexual behaviours amongst young adults with limiting disabilities, BMJ*). • The rate of unplanned pregnancy for women with PKU is the same as the general population. Women with PKU have the right to have sex and the right to have their reproductive rights supported in a non-discriminatory way. • I have spoken to many young women who are extremely emotional about the prospect of becoming pregnant. They are tearful and worried and sometimes express guilt. In the NSPKU survey it was very difficult to read that some women reported (anonymously) that these fears impacted their relationships and ability to have a sexual relationship *[References received but not reproduced in this table]*	

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		• In 2017 I interviewed a woman whose experience was featured anonymously in a booklet produced by NSPKU. She was early diagnosed and treated but her dietary treatment went off the rails as a teenager. She says she suffered very badly with depression in her teens and twenties. It was in this period that she conceived two children who have disabilities linked to Maternal PKU. The woman herself had disability linked to years of high levels. • From my experience of talking to women in the community, having generally poor metabolic control is a risk factor for unplanned pregnancy and poor outcomes. • Women with PKU who have had pregnancies affected by Maternal PKU are not at fault. This was not an outcome they chose. However there is guilt and emotional pain. Women have told me about losing pregnancies and the huge loss and pain they feel. A woman has described these issues as a "trauma". Women have told me of naming babies they have lost and grieving for them and marking the anniversaries of their loss. • Discussion about having children with disabilities or problems linked to PKU is also very difficult even within the PKU community. It can be difficult to acknowledge or discuss as women can feel guilt or shame. • Women have also told me that the support offered after birth is not enough. Many people with PKU experience symptoms when there is an abrupt change in their phenylalanine levels – for example headaches, tiredness and dizziness. Women with PKU who have had a baby are faced with the exhaustion of caring for their baby, trying to start breastfeeding, hormonal changes and an abrupt spike in their phenylalanine levels (from ultra low in pregnancy to uncontrolled or poorly controlled post-partum). Thereafter many women say they struggle with the work involved with maintaining a low phenylalanine diet and looking after their baby. • From my experience and knowledge I am aware that some women with PKU are vulnerable to struggling to cope once their baby is born. I am aware of women who have been hospitalised with post-natal depression. They may struggle to commence breast feeding and feel they can't cope. I am also aware of many women who had less severe problems, but which still impacted their experience of early motherhood. • The Committee should understand there can be quite severe problems within families affected by Maternal PKU. For example, women with PKU who have care needs related to their PKU or who have children with disabilities related to Maternal PKU. It is also possible for women with PKU to have children with PKU, where both the mother and the child have cognitive impairments or other issues related to PKU. I am aware of intensive social services involvement with some families with complex needs like this. However there a range of experiences within PKU, with children who thrive and have mothers who	

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		provide exemplary care. • There is evidence that women with chronic physical conditions are at higher risk perinatal mental illness from conception to one year after giving birth Chronic physical conditions and risk for perinatal mental illness: A population-based retrospective cohort study". *Hilary K. Brown , Andrew S. Wilton, Joel G. Ray, Cindy-Lee Dennis, Astrid Guttmann, Simone N. Vigod.* I am not aware there is a specific study of this issue for PKU but the risk is likely to be higher due to the particular stresses of pregnancy for women with PKU and the struggles that women with PKU report in maintaining dietary therapy. • It is well recognised that the pre-conception, pregnancy and early childhood years are crucial to children's health. Within this appraisal there needs to be an approach which is more sensitive to promoting good outcomes for women with PKU and their children and more sensitive to their own lived experiences. • It is my view that women should have access to sapropterin through their reproductive years. This will encourage women to have close ongoing relationships with their metabolic team, where women can be honest and supported to make educated choices about their sexual behaviour and plans to start a family. Maintaining good metabolic control in young women will reduce risk factors for unplanned pregnancy. Easy access to sapropterin prior to conception would make "pre-con" adherence less onerous and in my view would increase the number of women who conceive with controlled levels. I do not believe that this is a contentious view, for example the NHS England policy accepted that sapropterin makes it easier to sustain low levels, thus improving adherence and then outcomes "the diet becomes more manageable, thus improving dietary adherence." • Sapropterin should not be withdrawn immediately at birth; this is an inappropriate policy which fails to give women and children the support they need to make a good start. Women should not be forced to undergo a change of treatment regime at this very sensitive time. Women with a chronic condition like PKU, who are starting a family should be supported so their children can have a good "first 1000 days of life" which will improve their long term outcomes. • No country in the world has a Maternal PKU policy like the one adopted by NHS England. Nobody thinks its "optimal" but nobody has ever taken the step of replacing it with an "optimal" policy. NICE has a duty to women with PKU to resolve this. *[Confidential case study received but not reproduced in this table]* Additional comment – This case study is not a far outlier; the elements of emotional pain around baby loss, eating disorders and mental health problems as a young adult are all familiar to me from other women's stories known to me and the comments received in our NSPKU survey.	

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
41	I am nominated by the National Society for Phenylketonuria	The guidance manifestly fails to make a reasonable cost effectiveness analysis which takes into account the issues experienced by women with PKU and their children. This is because the ERG costs model ignores the harms experienced by women with PKU and their children. As the committee have asked for more comments and evidence on this issue I shall address this further: • Maternal PKU is a risk for miscarriage (e.g. *Jovanovic, 2011, Outcomes of pregnancy in maternal phenylketonuria (PKU): the north-east experience* – of 20 pregnancies in the PKU clinic, there were four early spontaneous abortions and four terminations of pregnancy. From our work with women we know these experiences can be emotionally devastating. I presume NICE STA is able to accord some QALY value to the loss of a pregnancy and I would invite the Committee to give this consideration. • Maternal PKU is a risk for cardiac problems which can be serious. The Jovanovic study referred to above refers to 1 of the 20 pregnancies resulting in a child being born with severe congenital cardiac abnormalities who died at 2 weeks. Many other studies show high rates of cardiac problems which will require ongoing medical attention. • Other physical problems referred to in the literature would require medical interventions, eg cleft palate, epilepsy, congenital cataracts. • Children affected by Maternal PKU are also at risk of issues such as microcephaly and learning disorders. These issues will have life-long costs, significantly affecting the quality of life of the individuals and their carers. Children can have a combination of problems which can be very disabling. I am aware of children affected by Maternal PKU who are not able to attend mainstream schools and will not live independently. At the milder side of the spectrum of outcomes, children may need significant extra input at school to assist with issues such as behavioural problems or learning difficulties. I would invite the Committee to reflect these issues into their costs modelling. • There is clear and well established evidence that low levels at conception and in early pregnancy improve outcomes which is acknowledged in the draft guidance but not carried through into the costs modelling or recommendations. • I would invite the Committee to include the assumption that improved access to sapropterin for women would improve outcomes within its costs modelling. • The Committee should account for the experience of women as well as their children. Sapropterin would make pre-conception diet less miserable and stressful. It could make controlling levels during pregnancy easier. It could ease women's experience post-partum. These experiences also have a value which should be recognised within the costs modelling.	Comments noted. The committee considered these responses and comments made at the committee meeting, and the guidance document has been updated. Sapropterin is recommended as an option for treating hyperphenylalaninaemia that responds to sapropterin in people with phenylketonuria (PKU), only if they are pregnant (from a positive pregnancy test until birth). See section 1.1 of the FAD. See also sections 3.3, 3.6, 3.19, 3.20, 3.24, 3.31, 3.37 of the FAD.
42	I am nominated	The process of developing this guidance was inadequate and discriminatory, particularly in the way	Comments noted. The committee considered these

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
	by the National Society for Phenylketonuria	in which is looked at groups of patients with protected characteristics. **I stress this is not a fault of individuals but the limitations of NICE processes.** • The guidance states it welcomes comments and further evidence about the subgroup affected by Maternal PKU. Many women have been upset and angry by the draft guidance. A female participant in our community meeting for adults to discuss the draft guidance referred to trauma associated with her experience of Maternal PKU. Many women were clearly very upset by it. Some women will have participated in the consultation process and we hope the Committee considers their evidence carefully. However I am also aware that many women find addressing these issues extremely upsetting and writing this down for NICE, within a context that many feel lacks any attempt at empathy – is a form of emotional labour which is too much. In my view it is likely that many women with important evidence to provide will not have participated. Some women have participated but found the whole process very distressing. • There should have been a more careful and sensitive enquiry about the issue of Maternal PKU within the process before this draft guidance was produced. The Committee meeting did not adequately discuss all the issues. This appraisal is multi-faceted, with PKU affecting different groups within the patient cohort in different ways, but the Committee meeting was faced with a fixed time slot which had to deal with all the issues within the allotted time. The Committee meeting itself was very well conducted within the constraints of the process and time allotted, but this left issues which were not properly examined. This process leaves some issues – particularly those affecting groups protected by the Equality Act – particularly disadvantaged. • Technical Engagement included only one consultant working with adults with PKU. It should have included other experts working with adults – for example a metabolic dietitian working with pregnant women with PKU. The metabolic dietitians working with adults– who are often female – typically work very closely with women with PKU in their pregnancies and often have a very good understanding of the lives of their patients. A wider (and less entirely male!) group of clinicians working with adult contributing to Technical Engagement would have helped bring a perspective which is closer to the reality of women's experiences. • The draft guidance refers to inadequacies in the Company's model as they relate to women with PKU and their children. The approach in the Company's model is obviously inappropriate and wrong - for example why are the reproductive years limited to 18-40 when this is not obviously not how women's bodies work? However at least the Company's model made an attempt to account for women's experience. The ERG model ignores the issue completely which makes their guidance manifestly unsound. NICE is the statutory body entrusted with the duty of developing accurate guidance on this issue. If the Company's model is not appropriate NICE is required to conduct its own enquiries to make reasonable evidence based guidance. This has not happened so far.	responses and comments made at the committee meetings, and the guidance document has been updated. Sapropterin is recommended as an option for treating hyperphenylalaninaemia that responds to sapropterin in people with phenylketonuria (PKU), only if they are pregnant (from a positive pregnancy test until birth). See section 1.1 of the FAD. See also sections 3.3, 3.6, 3.19, 3.20, 3.24, 3.31, 3.37 of the FAD.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		• The issues relating to adults with learning disabilities and cognitive impairments have not been adequately explored and this appears to have been due to the same problems with the process. The issue is "hiding in plain sight" when this guidance relates to a condition which causes brain damage. By definition, this cohort includes many adult patients with learning disabilities to various degrees but the issue is dealt with in passing. The consultation process made no attempt to be accessible to patients with learning difficulties or their carers who are often older people who do not use social media or computers.	
43	I am nominated by the National Society for Phenylketonuria	The guidance appears to recommend capping the dose at 10 mg/kg which is not appropriate. The discussion at 3.21 is about <u>average</u> doses which would be used in clinical practice, ie a range of doses, some below 10 mg/kg and some above 10 mg/kg in light of the license for the drug which allows doses from 5 mg/kg to 20 mg/kg. There is no logical basis for capping the dose at 10 mg/kg, rather than simply adopting an average dose across the patient group within the costs modelling. This was the approach adopted by NHS England. I am aware of patients who have had good clinical responses on low doses of sapropterin. These have been in patients funding the treatment privately where there is a significant need to be very careful about using the lowest possible dose. There is also an Irish paper which shows that some patients can be appropriately stabilised on lower doses of sapropterin *[Reference received but not reproduced in this table]* However some BH4 responsive patients will need higher doses – perhaps particularly if they have less mild PKU. These patients should not be excluded and may have significant benefits from the treatment. The guidance should allow clinicians the freedom to treat patients appropriately within the license. UK clinicians in the NHS will prescribe economically and appropriately. There is no basis for the distinction in the guidance between the average doses adopted for adults or children. It has not been rationalised.	Comments noted. The committee considered these responses and comments made during the committee meeting, and the guidance document has been updated. The dose for children can be increased above the starting dose of 10 mg/kg, only if target blood phenylalanine levels are not achieved at a dose of 10 mg/kg. So, it is recommended for treating PKU in people under 18, normally at a dose of 10 mg/kg. See sections 1.1, 3.11, 3.21, 3.28, 3.30 of the FAD**.**
44	I am nominated by the National Society for Phenylketonuria	The ERG model is not adequate. It does not capture many aspects of the benefits of the technology and this makes the guidance unsound: • At 2.2.3 of the ERG report is a statement that people with PKU have higher rates of physical co-morbidities and are at higher risk of chronic disease. The ERG model did not include this. • The Committee did not include an assumption about health care costs related to treating the issues listed in 2.2.3 of the ERG report. If it is included, to what extent? • The NICE reference case states "all direct health effects, whether for patients, or when relevant, carers" should be considered. Carer disutility was not included in the cost effectiveness calculations for adults or for children. Why? • The cost calculation did not include a valuation of the cost of care delivered by family	Comments noted. The issues of costs of long-term brain damage, carers' costs, carer disutilities and comorbidities associated are discussed in section 3.23 of the FAD. The risk of irreversible brain damage reduces with age, particularly after brain development is complete. So the adverse effects of being unable to follow the protein-restricted diet are considerably reduced in adults compared with the risks in childhood. Adults may still gain considerable benefit from sapropterin because of fewer symptoms related to raised phenylalanine levels, without having to follow the protein-restricted diet as strictly. However, these benefits are included in the economic modelling. Also, in adults the weight-based dose together with the higher average mg/kg dose results in costs that are considerably higher than in children, but the benefits are not correspondingly higher for

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		members which might otherwise have been provided by the NHS or personal social services as suggested by 5.5.13 of the Process Guide. Many adults rely upon others to help them adhere to dietary treatment or to manage the effects of high phenylalanine (e.g. tremors, forgetfulness). If informal family care was removed, the costs of supporting these individuals via standard dietary treatment would be substantial. • The draft guidance makes contradictory, unclear and evidentially unsound assumptions about long-term brain damage. NICE did not even include a risk of long-term brain damage in adults to "around 25" within its costs modelling for the over 18s. • The ERG model does not include the cumulative risks associated with high phenylalanine or a poor diet. This is not a logical approach to take when the ERG report states that high blood phe concentrations are linked to an increased risk of chronic diseases. There is also clear evidence about the cumulative harm caused by exposure to high phenylalanine levels. • Healthcare costs for treating PKU and the problems associated with PKU appear to have been underestimated or left out entirely. • The ERG report notes that impaired functioning can impair the ability to reduce phenylalanine levels through diet (2.2.1). Did the cost calculation for adults include an assumption that some adults patients with symptoms cannot "reverse" them and that they are therefore permanent? • NICE has recognised that early control of phe levels - before conception - would reduce the risks to unborn children (3.2). It is noted by NICE that there is a policy allowing for pregnant women with PKU to access sapropterin but that it is "suboptimal" due to the delays in access in early pregnancy being harmful. The decision to ignore the harms suffered by women and their children is therefore not logical. • The Committee has not appropriately contextualised its approach to uncertainty in the evidence. This appraisal concerns a sub-set of a rare disease (BH4 responsive PKU). Within this appraisal are other issues concerning even smaller sub-sets of patients – pregnant/maternal women with PKU, or patients with PKU who have significant care needs. These areas are inherently hard to study or will not ever be a target for significant research. NICE methods guide states that in areas of uncertainty in costs modelling "the Committee is aware that the evidence base will necessarily be weaker for some technologies, such as technologies used to treat patients with very rare diseases". The issues in this appraisal are at the far parameters of low prevalence/lower research base of NICE STA. If NICE is to adopt an expectation for gilt-edged evidence for these issues it will inevitably lead to recommendations which are unsound. I would invite the Committee to attempt to overcome these obstacles using feedback from the consultation and other available evidence.	adults. Even taking into account any uncaptured benefits in adults, the cost-effectiveness estimates are substantially higher than what NICE considers an acceptable use of NHS resources. So, it is not recommended for adults aged over 21. See sections 3.1, 3.2, 3.6, 3.13, 3.23, 3.29, 3.30, 3.34, 3.35, 3.36 and 3.38 of the FAD.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
45	I am nominated by the National Society for Phenylketonuria	The Committee has not adequately addressed its obligation under the Equality Act. There are significant failings in the guidance. In particular • The decision making around women with PKU and their children does not adequately consider their needs. The decision to not make recommendations in relation to this group is not logical in light of the evidence or adequately explained. Both women with PKU, and their disabled children, are protected groups under the Equality Act. • The decision to recommend withdrawing treatment at the age of 18, and not recommending the treatment for adults over the age of 18, discriminates between groups by reason of age. The clinical reasoning for the decision is manifestly inadequate and the costs modelling relied upon by NICE is unsound. • The decision making in the ACD reveals a "blind spot" around adults with PKU with significant care needs. It acknowledges the existence of adults with brain damage and cognitive issues and yet consideration of their situation is lacking. The costs modelling does not account for this group adequately. These learning disabled adults are a protected group under the Equality Act and the process of developing the guidance and making recommendations was not adequate in relation to this group. • The paragraph on "Equalities" at 2.25 does not meet the requirements of the Equality Act or address health inequalities. It lists various protected groups and simply states that it could not identify any group of adults for whom a positive recommendation could be justified given the cost effectiveness estimates in adults. This statement is inadequate as it does not address whether the cost effectiveness estimates are relevant to the groups in question. The decision making does not meet the standards required of the public sector equality duty.	Comments noted. The committee was aware that age-based recommendations must be objectively justified, and they should be avoided when possible. It considered the justification in this case is the need to secure acceptable cost efficacy in the interests of the NHS as a whole. Age itself is both an indicator of potentially greater benefit, coupled with lower cost of treatment. The reason for the cost-effectiveness estimates being higher in the over 18 population are explained in this guidance, as are the reasons for having 22 as the age for stopping treatment. The committee explored alternative approaches but could not find any better alternative to this approach. See sections 3.32 and 3.36 of the FAD. NICE is aware that a recommendation for use during pregnancy is necessarily only of benefit to people who become pregnant. This is permitted by s.17(6)(a) of the Equality Act 2010. See section 3.37 of the FAD.
46	I am a clinical expert nominated by RCP	I have concerns about the need to stop sapropterin treatment at the age of 18. I can understand the argument that it is most important to obtain strict metabolic control in childhood, as the risk of irreversible damage to the brain and permanent loss of IQ is reduced after the age of 10 and is not present in adults. I also agree that treating adults would not be cost effective as the potential benefits from treatment are much less and the patients weigh much more. However, neither of these considerations would lead to a decision to stop treatment at the age of 18. The primary aim of any treatment for PKU must be to prevent irreversible brain damage, but if the funding decision is primarily based on cost effectiveness, then there would be a weight at which treatment was no longer cost-effective. When children reach that weight (perhaps with the proviso that they are also more than 12 years old to definitely prevent loss of IQ points) sapropterin would be stopped. If the goal is to ensure optimum outcomes by treating young people until neurodevelopment has finished, then you wuld continue beyond 18, perhaps until the age of 25.	Comments noted. The committee considered these responses and comments made during the committee meeting, and the guidance document has been updated. See section 1.1 of the FAD The committee recognised that stopping treatment and relying on diet alone at 18 years old is not ideal. It would benefit young adults if treatment with sapropterin could be continued for as long as possible during final brain development and transition into adulthood. The maximum age at which sapropterin can be considered a cost-effective use of NHS resources is 21. However, for this to be cost effective people would need to continue the dose they were having when they were under 18. In practice this may mean that some young adults may need more dietary control alongside sapropterin between the ages of 18 and 21 than they would

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		The decision to recommend stopping sapropterin treatment at the age of 18 seems arbitrary and will coincide with a particularly vulnerable period in these young peoples lives. They will be their final year of secondary education, and in many cases will be preparing for exams which will play a large role in determining their futures. Abrupt withdrawal of sapropterin, with the concomitant need for more severe dietary restriction in order to maintain target phenylalanine levels, at this time would be needlessly distressing and disruptive, and might well end up having a real effect on the subsequent course of their lives. I think more sensitive consideration needs to be given to when and how treatment would be withdrawn	with a higher dose. See sections 3.6, 3.30, 3.34, 3.36 and 3.38 of the FAD.
47	I am a clinical expert nominated by RCP	I have concerns about the decision not to recommend sapropterin for use in women planning pregnancy and in pregnant women with PKU. Although there may be limited evidence on the use of sapropterin in pregnancy, there is a wealth of evidence concerning the teratogenic effects of phenylalanine and the need for women with PKU to obtain strict metabolic control throughout pregnancy. Given that pregnancy is time limited and that the effects of high phenylalanine levels on the children of mothers with PKU are potentially so severe, there should be no question of the cost-effectiveness of sapropterin in this setting. Women with PKU who are planning pregnancy, and the healthcare professionals looking after them need access to every means possible of maintaining phenylalanine levels within the target range for pregnancy. In my view sapropterin should be available to treat all women with PKU who are sapropterin responsive whilst they are trying to maintain phenylalanine levels in the pregnancy range, both during the preconception period and throughout pregnancy. I do not, however, think that sapropterin should be made available to all females of childbearing age whether or not they are currently pregnant or planning pregnancy. Most of these women would have phenylalanine levels well above the pregnancy range and would still need to make significant modifications to their diets when planning pregnancy, or if they had an unplanned pregnancy. The key factor in ensuring optimal pregnancy outcomes for women with PKU is education about the need to plan pregnancy and the availability of as many interventions as possible to help them maintain target phenylalanine levels when deciding to go on a preconception or pregnancy diet.	Comments noted. The committee considered these responses and comments made at the committee meeting, and the guidance document has been updated. Sapropterin is recommended as an option for treating hyperphenylalaninaemia that responds to sapropterin in people with phenylketonuria (PKU), only if they are pregnant (from a positive pregnancy test until birth). See section 1.1 of the FAD. See also sections 3.3, 3.6, 3.19, 3.20, 3.24, 3.31, 3.37 of the FAD.
48	I am a clinical expert nominated by RCP	I have concerns about the lack of clear criteria concerning sapropterin responsiveness and the lack of definition of what constitutes a satisfactory response to treatment. One of the major issues in using sapropterin to treat PKU is that it has different effects in different patients. It is important to precisely define which patients are to be considered responsive to sapropterin. This involves describing the method of testing as well as what constitutes an adequate response in terms of lowering phenylalanine and/or increasing natural protein intake. Sapropterin is used as an adjunct to diet. Dietary treatment on its own can be used to achieve target phenylalanine levels in all patients, although this can be very challenging. Therefore, for different patients the goals of adding sapropterin to dietary treatment are different. For some, the goal will be to reduce phenylalanine levels into the normal range whilst for the majority, the goal will be to allow patients to maintain target phenylalanine levels with less dietary restriction. Because of this it is also very important to define criteria for what constitutes a satisfactory long-term response to sapropterin.	Comments noted. This committee considered this outside the remit of this appraisal. See section 3.28 of the FAD.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		Without clearly defined definitions of responsiveness and response, it will be very difficult to translate any NICE recommendations into clinical practice. The final recommendations need to address these issues in detail. This has previously been done by a policy working group convened by NHSE and the committee might find it very useful to look at the NHSE policy proposal which resulted from that work.	
49	I am a clinical expert nominated by BIMDG	I am concerned the age chosen when patients will have to stop Sapropterin (18yrs) will present a particular challenge for young adults with PKU. If they are to retain good Phenylalanine control in adulthood they will have to return to a much stricter diet when they stop Sapropterin at a time when they have just transitioned/are transitioning to adult services. Transition already represents a particularly challenging period and young adults are at risk of disengaging from clinical services. I would recommend, for patients commenced on Sapropterin, that the age of withdrawal of treatment should be extended (for instance to 25yrs)	Comments noted. The committee considered these responses and comments made during the committee meeting, and the guidance document has been updated. See section 1.1 of the FAD The committee recognised that stopping treatment and relying on diet alone at 18 years old is not ideal. It would benefit young adults if treatment with sapropterin could be continued for as long as possible during final brain development and transition into adulthood. The maximum age at which sapropterin can be considered a cost-effective use of NHS resources is 21. However, for this to be cost effective people would need to continue the dose they were having when they were under 18. In practice this may mean that some young adults may need more dietary control alongside sapropterin between the ages of 18 and 21 than they would with a higher dose. See sections 3.6, 3.30, 3.34, 3.36 and 3.38 of the FAD.
50	I am a clinical expert nominated by BIMDG	The introduction of a limit of 10mg/kg will exclude some children who are Sapropterin responsive from treatment – evidence suggests that more patients will respond to doses of 20mg/kg than 10mg/kg [Muntau et al 2019], although the proportion of patients who only respond to 20mg/kg will depend on individual genotype and method of response testing. Thus, the numerical impact of this on under 18yr olds in the UK is unclear.	Comments noted. The committee considered these responses and comments made during the committee meeting, and the guidance document has been updated. The dose for children can be increased above the starting dose of 10 mg/kg, only if target blood phenylalanine levels are not achieved at a dose of 10 mg/kg. So, it is recommended for treating PKU in people under 18, normally at a dose of 10 mg/kg. See sections 1.1, 3.11, 3.21, 3.28, 3.30 of the FAD.
51	I am a clinical expert nominated by BIMDG	Definitions of sapropterin responsiveness and the methodology for testing sapropterin responsiveness are highly variable. It is important that a robust and practical protocol for testing responsiveness is adopted as part of this guidance – lack of such guidance may result in patients being inappropriately labelled as responsive (thus reducing cost effectiveness) and significant inequity of access.	Comments noted. This committee considered this outside the remit of this appraisal. See section 3.28 of the FAD.
52	British Inherited Metabolic Diseases Group dietetic group	There are 3 questions that are asked: 1. Has all the relevant evidence been taken into account? 2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? 3. Are there any aspects of the recommendations that need particular consideration, to avoid unlawful discrimination?	Comments noted. The committee considered these responses and comments made during the committee meeting, and the guidance document has been updated. See section 1.1 of the FAD The committee recognised that stopping treatment and relying on diet alone at 18 years old is not ideal. It would

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		The document recommendations fall short of fulfilling these questions. On the basis of unlawful discrimination stopping any drug at 18 years of age is detrimental to a person's wellbeing and coercive. This recommendation shows a complete lack and disregard of any understanding towards the treatment of phenylketonuria (PKU). The committee making these recommendations have neglected the relevant evidence for those adults at 18 years or older. This decision will have a devasting impact on a young person it potentially will ruin their life chances, as sustaining a restricted diet after 18 is not feasible or sustainable and the reasoning made by NICE flawed. There is agreement that sapropterin is clinically appropriate, effective and beneficial for people with PKU that respond to sapropterin; why should this benefit be stopped at 18 years of age when treatment is for life. There is evidence to refute the statement 'the dose of sapropterin is based on weight so costs are higher for adults than children but there is no extra increase in quality of life to offset these costs.' Yes, it is true costs are lower for children, but to make a statement that it can be withdrawn as it has not benefit to quality of life (QoL) is short sighted. There is overwhelming evidence to suggest the contrary, irreversible brain damage is avoided for all children if treatment is started on time. However, the pathology for brain dysfunction continues throughout life, with evidence [1] showing higher blood phenylalanine concentrations are responsible for neurocognitive delay, which impacts on the quality of life. Adults non-compliant to diet therapy have a range of neurological, psychosocial, and physical dysfunctions. This evidence cannot be ignored, dismissed or compared to a price tag.	benefit young adults if treatment with sapropterin could be continued for as long as possible during final brain development and transition into adulthood. The maximum age at which sapropterin can be considered a cost-effective use of NHS resources is 21. However, for this to be cost effective people would need to continue the dose they were having when they were under 18. In practice this may mean that some young adults may need more dietary control alongside sapropterin between the ages of 18 and 21 than they would with a higher dose. See sections 3.6, 3.30, 3.34, 3.36 and 3.38 of the FAD.
53	British Inherited Metabolic Diseases Group dietetic group	Has all the relevant evidence been taken into account? Evidence for poor dietary adherence leading to high blood phenylalanine concentrations and sub optimal neurocognition. 1. Sapropterin is only available as an adjunctive therapy for 20 to 30 % of the UK PKU population. The majority of patients have no alternative choice. Limiting drug therapy for those with a choice is unfair. 2. Sapropterin as NICE have stated reduces blood phenylalanine concentrations allowing a less restricted diet, and the benefits of lower blood phenylalanine are reducing neurocognitive damage, with evidence showing higher blood phenylalanine concentrations lead to decreased neurocognition 3. Without sapropterin diet therapy is rigorous, restrictive and lifelong. There is compelling evidence that compliance, together with increased phenylalanine concentrations deteriorates with age. 4. Dietary treatment is strict and demanding, mild cognitive abnormalities are recognised from a young age and these affect QoL of patients and families. Bosch et al 2015 [2] describes the treatment of sapropterin compared to dietary treatment alone, with adults being less aggressive and improve cognition, with less social impact and greater dietary freedom. 5. Although the early initiation of dietary treatment prevents the most severe psychiatric and neurological symptoms, especially intellectual disability; behavioural and emotional	Comments noted. The committee considered the responses to the ACD on this theme and the comments made at the committee meeting. The risk of irreversible brain damage reduces with age, particularly after brain development is complete. So the adverse effects of being unable to follow the protein-restricted diet are considerably reduced in adults compared with the risks in childhood. Adults may still gain considerable benefit from sapropterin because of fewer symptoms related to raised phenylalanine levels, without having to follow the protein-restricted diet as strictly. However, these benefits are included in the economic modelling. Also, in adults the weight-based dose together with the higher average mg/kg dose results in costs that are considerably higher than in children, but the benefits are not correspondingly higher for adults. Even taking into account any uncaptured benefits in adults, the cost-effectiveness estimates are substantially higher than what NICE considers an acceptable use of NHS resources. So, it is not recommended for adults aged over 21. See sections 3.1, 3.2, 3.6, 3.13, 3.23, 3.29, 3.30, 3.34, 3.35, 3.36 and 3.38 of the FAD.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		problems are still described in many continuously treated children and adolescents. 6. The impairment of these mental processes leads to inattention, hyperactivity and impulsiveness in early treated PKU children. Other behaviours have been cited such as anxiety, phobias, depression, social isolation and psychosomatic difficulties. 7. Less adherence to treatment with consequent higher blood phenylalanine concentrations are partially responsible for these neuropsychological symptoms 8. There is evidence to suggest mild intellectual disability (albeit not as severe as untreated PKU subjects) is found in early treated PKU children and continues lifelong. 9. There are several studies all showing behaviour and emotional problems in early treated children and adolescents have been reported (Vieira 2018). Parents report attention problems and hyperactivity with nonadherent to treatment and intellectually low performing patients with PKU. 10. The proposed mechanisms for these impairments include dopamine depletion and white matter pathology. Neuroimaging studies demonstrate high signal intensity in the periventricular while matter observed in PKU patients. Research shows that this pathology is associated with metabolic control and possibly only reversed with a strict low phenylalanine diet [1, 3] 11. Brumm et al [4]shows psychiatric and psychological problems are well documented across the lifespan of early treated PKU patients. Common problems: attention deficient, poor school performance, low achievement motivation, decreased social competence, lower autonomy and self-esteem. Moving into adulthood, despite early treatment these issues continue: low self-esteem, a lack of autonomy, depression, anxiety, phobias, decreased positive emotions, immature social skills and social isolation. The correlation between the level of metabolic control and severity of symptoms suggests a biological basis of psychiatric dysfunction. 12. Although it is difficult to quantify, additional psychosocial factors such as the burden of living with a chronic disorder may contribute to psychological and psychiatric outcome in PKU [5, 6]. 13. Treatment is the same for those at all ages and therefore, cannot be discriminated on the basis of age. The practicality of sustaining treatment becomes more difficult and almost impossible for many with PKU. To remove a drug treatment at any age is subjecting this group of patients to a deterioration in neurocognition.	The committee was aware that age-based recommendations must be objectively justified, and they should be avoided when possible. It considered the justification in this case is the need to secure acceptable cost efficacy in the interests of the NHS as a whole. Age itself is both an indicator of potentially greater benefit, coupled with lower cost of treatment. The reason for the cost-effectiveness estimates being higher in the over 18 population are explained in this guidance, as are the reasons for having 22 as the age for stopping treatment. The committee explored alternative approaches but could not find any better alternative to this approach. See sections 3.32 and 3.36 of the FAD.
54	British Inherited Metabolic Diseases Group dietetic group	The evidence from studies in table 1 and 2 are overwhelming in their findings a) dietary adherence decreases over time b) b) phenylalanine concentrations deteriorate over time c) neurological damage is continuous increasing with higher blood phenylalanine concentrations d) quality of life due to neurological dysfunction is detrimental to the patient and family Neurological damage is a constant clinical concern, with a proven pathology. This damage increases with poor metabolic control which is more likely in those over the age of 10 years with many adults unable to sustain dietary treatment and the required low blood phenylalanine concentrations within the target therapeutic range.	Comments noted. The committee considered the responses to the ACD on this theme and the comments made at the committee meeting. The risk of irreversible brain damage reduces with age, particularly after brain development is complete. So the adverse effects of being unable to follow the protein-restricted diet are considerably reduced in adults compared with the risks in childhood. Adults may still gain considerable benefit from sapropterin because of fewer symptoms related to raised phenylalanine levels, without having to follow the protein-restricted diet as strictly. However, these benefits are included in the economic modelling. Also, in adults the

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		It would be unethical to withdraw treatment at any age, if it is beneficial. There is a large body of evidence which has been disregarded. To state that the quality of life will not be further enhanced after 18 years of age is factually wrong. In all the other countries using sapropterin, withdrawing treatment, has never been considered a viable or ethical policy. The evidence from NICE shows that those taking sapropterin can achieve target blood phenylalanine concentrations avoiding the consequences of damaging higher blood phenylalanine levels. NICE acknowledge lower IQ scores and neuropsychological impairments are present in PKU patients, therefore, to stop treatment at 18 years would lead inevitably lead to a deterioration in mental wellbeing and quality of living. To make the statement there is no risk of long term brain damage in adults is completely misguided and unsubstantiated, the evidence from Table 1 and 2 repeatedly shows nonadherence to diet, becomes harder with age, and the majority of teenagers and adults have phenylalanine concentrations outside the therapeutic range with evidence based research to show brain damage is continuous impacting life choices.	weight-based dose together with the higher average mg/kg dose results in costs that are considerably higher than in children, but the benefits are not correspondingly higher for adults. Even taking into account any uncaptured benefits in adults, the cost-effectiveness estimates are substantially higher than what NICE considers an acceptable use of NHS resources. So, it is not recommended for adults aged over 21. See sections 3.1, 3.2, 3.6, 3.13, 3.23, 3.29, 3.30, 3.34, 3.35, 3.36 and 3.38 of the FAD.
55	British Inherited Metabolic Diseases Group dietetic group	Routine monitoring of emotional and behavioural and psychosocial symptoms in individuals with PKU is necessary together with longitudinal studies to evaluate the impact of new and emerging therapies. These reported clinical findings have a significant lifelong impact on the quality of life and social status of patients.	Comments noted.
56	British Inherited Metabolic Diseases Group dietetic group	On behalf of the British Inherited Metabolic Disease -Dietitians Group, we strongly recommend the evidence is reappraised in the light of peer review publications. Any treatment that can reduce blood phenylalanine concentrations prevents long term brain deterioration, and the associating insidious detriments to daily living. *[References received but not reproduced in this table]* *[Table 1 and 2 received but not reproduced in this table]*	Comments noted. The committee considered the responses to the ACD on this theme and the comments made at the committee meeting. The risk of irreversible brain damage reduces with age, particularly after brain development is complete. So the adverse effects of being unable to follow the protein-restricted diet are considerably reduced in adults compared with the risks in childhood. Adults may still gain considerable benefit from sapropterin because of fewer symptoms related to raised phenylalanine levels, without having to follow the protein-restricted diet as strictly. However, these benefits are included in the economic modelling. Also, in adults the weight-based dose together with the higher average mg/kg dose results in costs that are considerably higher than in children, but the benefits are not correspondingly higher for adults. Even taking into account any uncaptured benefits in adults, the cost-effectiveness estimates are substantially higher than what NICE considers an acceptable use of NHS resources. So, it is not recommended for adults aged over 21. See sections 3.1, 3.2, 3.6, 3.13, 3.23, 3.29, 3.30, 3.34, 3.35, 3.36 and 3.38 of the FAD.
57	National Society	The recommendation that sapropterin should be used until the age of 18 and then stopped is	Comments noted. The committee considered these

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
	for Phenylketonuria and Metabolic Specialist Dietitian at North Bristol NHS Trust	inappropriate and dangerous. The reasons are set out below: Difficulties Starting diet only treatment at age 18 (and difficulties experienced by all on PKU diet): The European Guidelines for Diagnosis & Management of PKU state that treatment should be lifelong (van Spronsen et al 2017), so a patient stopping sapropterin at age 18 would need to start dietary treatment. The diet is commonly restricted to about 10g protein per day (Ford et al 2018), and protein containing foods are counted and measured down to 0.3g protein per serving. The complexity of the diet is beyond any other dietary regimen and has evolved over 20-30 years and details have only just been agreed by specialists (Evans et al 2019). It is necessary to plan, shop for ingredients, weigh foods and cook/prepare foods with great care. Baking with low protein products and no egg takes quite some skill and not everyone acquires these skills. The time commitment needed for a low protein diet is considerable and has been measured. A recent NHS Commissioning policy noted that: “Families and patients have been found to spend on average 19 hours per week on dietary compliance, thus affecting every aspect of life and testing patient’s self-control (MacDonald A et al 2016)” The above relates to people who did not have impaired intellectual or executive functioning. In individuals with impaired neurocognitive functioning (a recognised result of undertreated PKU, well evidenced by many including Palermo et al 2017)) the time taken to manage the diet is longer. Further evidence shows that, in order to achieve the best health outcomes for adults self-managing their PKU, part time working, and flexible working patterns were the only ways to achieve good control in a group of adults with PKU (Riva et al 2017). Someone stopping sapropterin and starting diet would be compromising their ability to attend college full time or do a full-time job. The current treatment regimen consists of specialist low protein products to provide energy and variety and a protein substitute providing amino acids without the phenylalanine – these are only available on prescription. In a peer review paper (Ford et al 2019) reporting access issues to products via the NHS 59% of responses (over 250 respondents) showed difficulty accessing basic low protein foods (bread, pasta) and 33% protein substitute. 36% of responses said problems had occurred for over a year. 18% reported that the local NHS authority had refused, restricted or had a policy to block treatment access; 27% cited GPs declining requests or restricting prescription amounts. This all equates to treatment disruption for patients with PKU in England, and poorer outcomes for all. Patients experience food insecurity and treatment insecurity on an ongoing basis. Aspartame – is a phenylalanine ester and thus must be avoided in PKU. The additional scrutiny of checking all food ingredient labels for aspartame in food, drinks and drugs intensifies the complexity of management, so this is a further difficulty for PKU patients of all ages. In peer reviewed evidence, Newbould and team (2021) reported that 74% of 200 PKU patients surveyed had accidentally ingested aspartame. 23% respondents had been prescribed medicines containing	responses and comments made during the committee meeting, and the guidance document has been updated. See section 1.1 of the FAD The committee recognised that stopping treatment and relying on diet alone at 18 years old is not ideal. It would benefit young adults if treatment with sapropterin could be continued for as long as possible during final brain development and transition into adulthood. The maximum age at which sapropterin can be considered a cost-effective use of NHS resources is 21. However, for this to be cost effective people would need to continue the dose they were having when they were under 18. In practice this may mean that some young adults may need more dietary control alongside sapropterin between the ages of 18 and 21 than they would with a higher dose. See sections 3.6, 3.30, 3.34, 3.36 and 3.38 of the FAD. The risk of irreversible brain damage reduces with age, particularly after brain development is complete. So the adverse effects of being unable to follow the protein-restricted diet are considerably reduced in adults compared with the risks in childhood. Adults may still gain considerable benefit from sapropterin because of fewer symptoms related to raised phenylalanine levels, without having to follow the protein-restricted diet as strictly. However, these benefits are included in the economic modelling. Also, in adults the weight-based dose together with the higher average mg/kg dose results in costs that are considerably higher than in children, but the benefits are not correspondingly higher for adults. Even taking into account any uncaptured benefits in adults, the cost-effectiveness estimates are substantially higher than what NICE considers an acceptable use of NHS resources. So, it is not recommended for adults aged over 21. See sections 3.1, 3.2, 3.6, 3.13, 3.23, 3.29, 3.30, 3.34, 3.35, 3.36 and 3.38 of the FAD.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		aspartame and 75% said that medicines were not checked by medics when prescribed. Further evidence about how difficult the diet can be, is published evidence following analysis of over 460 standard food items, reported that 55% of food labels were unclear (Kravela et al 2020) Finally: data less than a year-old shows that the majority of English adults (with or without PKU) are overweight or obese; 67% of men and 60% of women. If the general population cannot manage their own energy intake to match energy expenditure (a well understood concept), how can people with PKU restrict their diet to an average of 10g protein daily, which seems to be undermined by a number of systemic failings in the NHS and public health strategy? There is clear evidence globally and in the UK about worsening metabolic control as PKU patients become adolescents and adults (Walter et al 2002, Mundy et al 2002, Walter & White 2004 and Ahring et al 2011 all include UK based adult patients). NICE does not provide any evidence that the future would be different and that 18-year-olds stopping sapropterin would have safe metabolic control and good outcomes in this treatment pathway. An example in my clinical experience is women with mild PKU are taught to restart diet – they may have no experience of implementing a PKU diet and needs to learn the diet – this can take multiple (50+) hours of intense work and dedication on the part of all – these women are not true proxies for this sapropterin to diet scenario, as the pregnancy diet is a temporary intervention only. Patients returning to diet, in my clinical experience, generally do not succeed on an ongoing basis. There is no evidence to suggest that this unethical proposal NICE has for offering sapropterin to responsive patients until the age of 18 would enable them to continue safely into adulthood with good metabolic control, and good outcomes. All evidence suggests the opposite. *[References received but not reproduced in this table]*	
58	National Society for Phenylketonuria and Metabolic Specialist Dietitian at North Bristol NHS Trust	The statements on the risks of long-term brain damage in adults are inconsistent and lack robust evidence or investigation. “Clinical experts explained…..In adults, high Phe concentrations can result in short-term symptoms, which are considered reversible by lowering Phe levels through diet.” The literature suggests that white matter changes caused by high phe in the brains of adults with PKU is more reversible than brain damage incurred in children. However, there is no conclusive evidence that brain damage in adults is fully reversible. For example, Cleary in published on this 26 years ago, and 2 months ago, further imaging evidence is provided by Clocksin et al, 2021 in MGM) have found improvements following phe level reduction in adults. Even after improvement, white matter integrity in the PKU patients in these studies continued to be compromised relative to healthy non-PKU individuals. In practice, there is no evidence of successful cohorts of patients (except preconceptually and in pregnancy) returning to diet and regaining control of their PKU – there is evidence of patients who	Comments noted. The committee considered the responses to the ACD on this theme and the comments made at the committee meeting. The risk of irreversible brain damage reduces with age, particularly after brain development is complete. So the adverse effects of being unable to follow the protein-restricted diet are considerably reduced in adults compared with the risks in childhood. Adults may still gain considerable benefit from sapropterin because of fewer symptoms related to raised phenylalanine levels, without having to follow the protein-restricted diet as strictly. However, these benefits are included in the economic modelling. Also, in adults the weight-based dose together with the higher average mg/kg dose results in costs that are considerably higher than in children, but the benefits are not correspondingly higher for

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		were unable to (Bik-Multanowski 2008), so the reversibility of white matter damage in adults with PKU is entirely theoretical and not evidence based. Adult patients who stop the PKU diet experience poor executive functioning, information processing (worse reaction times, sustained attention, poor working memory) and mood (increased inhibition, anxiety, depression and low self-esteem) compared with adults who have continued phenylalanine restriction throughout life and also metabolically healthy controls. However, even adults with continuously treated Pku on diet, do see experience decline in their executive functions. Other study data distinguishes specific poor executive function linked to concurrent metabolic control – ie that in adulthood - Romani et al 2017 and 2019 – such as sustained attention. If adults have poor sustained attention, how can they reverse their white matter changes by successful dietary implementation in a regimen that is complex and when prescribing practices, labelling legislation and public health practices do not support this. Finally: case control study data evidences adults with PKU have compromised social cognition – this in itself may see inconsequential – combined with the need for ongoing self-advocacy for optimal outcomes for an intrusive treatment for a rare disease, then it contributes to difficulties with the diet – people cannot assert their needs in various life situations and thus fall out of control (negotiating GP, pharmacies, work situations etc). *[References received but not reproduced in this table]*	adults. Even taking into account any uncaptured benefits in adults, the cost-effectiveness estimates are substantially higher than what NICE considers an acceptable use of NHS resources. So, it is not recommended for adults aged over 21. See sections 3.1, 3.2, 3.6, 3.13, 3.23, 3.29, 3.30, 3.34, 3.35, 3.36 and 3.38 of the FAD.
59	National Society for Phenylketonuria and Metabolic Specialist Dietitian at North Bristol NHS Trust	Clinical experts noted that just over 50% of adults with PKU are on a protein- restricted diet, while about 30% of adults have stopped their diet and the other 20% have difficulties maintaining it. I am unaware of any evidence, nor was it provided, which supports these figures; there is evidence to the contrary. Incidence and prevalence of PKU in England, compared to the 2,000 people NICE mentions currently in PKU care and the clinical expert's comments are all inconsistent. Expected number of patients: NICE notes that 2,000 patients are receiving PKU care in the NHS currently. Yet >2,400 have been diagnosed by the Public Health England Newborn screening programme since 1969. Basic diagnostic tests were used from 1951-1969 - 1,000 babies would have been born then and diagnosed then or subsequently via sibling screening or investigations. How can clinical experts know if 50% of these adults with PKU are on diet if they are not in PKU care? People who are not in follow up will not be on diet. 1. Many adults with PKU are no longer followed up by specialists. 2. Patients were discharged in the past by medics who believed their brains had finished developing and PKU treatment cessation was safe and appropriate from the age of 4 through to the age of 18-19 (active discharges were happening from all metabolic care as recently as 10 years ago). 3. Patients are lost to follow up still and on an ongoing basis due to poor transition arrangements (I have contacts with these patients on NSPKU helpline).	Comments noted. Section has been amended. Committee noted NHSE figures, and comments from clinical experts that around 50% of adults with PKU are on diet. See section 3.5 of the FAD. The risk of irreversible brain damage reduces with age, particularly after brain development is complete. So the adverse effects of being unable to follow the protein-restricted diet are considerably reduced in adults compared with the risks in childhood. Adults may still gain considerable benefit from sapropterin because of fewer symptoms related to raised phenylalanine levels, without having to follow the protein-restricted diet as strictly. However, these benefits are included in the economic modelling. Also, in adults the weight-based dose together with the higher average mg/kg dose results in costs that are considerably higher than in children, but the benefits are not correspondingly higher for adults. Even taking into account any uncaptured benefits in adults, the cost-effectiveness estimates are substantially higher than what NICE considers an acceptable use of NHS resources. So, it is not recommended for adults aged over 21.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		4. The treatment status of any of the above groups of adults in the UK cannot possibly be known as no arrangements are in place to find them. 5. The percentages mentioned do not even apply to adult patients in clinics as there are insufficient blood phenylalanine results or published data to support this. There is a responsibility of health care providers in the UK to make provision for treatment for all adults with PKU and optimise the outcomes. NICE and/or its clinical expert has overestimated the use of diet amongst adults with PKU in the UK and thus ignored potential adverse outcomes of those not on diet. Finally: in my clinical experience the 50% of adults on diet and "not struggling" does not relate to adults with PKU, even those receiving metabolic follow up. In published survey data (Ford et al 2018) 73% of adults (n=209/286) said they found dietary management difficult. Eg female patients in Bristol – are rarely able to take the prescribed dose of protein substitute, rarely send bloodspots. An example: patient P never misses any appointments; she tries very hard to have a low protein diet but she takes 5 out of 21 doses of her amino acids each week Taking protein substitute is fundamental to the PKU diet regimen. She is not alone in this and both direct experience of patients in my NHS work, work with those seeking help from NSPKU, and published evidence backs this up. Thus I refute the clinical expert comments, from a "whole UK PKU cohort" perspective and within clinical experience perspective. *[References received but not reproduced in this table]*	See sections 3.1, 3.2, 3.6, 3.13, 3.23, 3.29, 3.30, 3.34, 3.35, 3.36 and 3.38 of the FAD.
60	National Society for Phenylketonuria and Metabolic Specialist Dietitian at North Bristol NHS Trust	Consideration of Maternal PKU Syndrome: NICE acknowledges that maternal phenylketonuria (PKU) syndrome is caused by high blood phenylalanine (Phe) levels during pregnancy having a teratogenic effect on the developing foetus which can result in intrauterine growth retardation, facial dysmorphism, developmental delay, intellectual disabilities, microcephaly and congenital heart disease (CHD). In my role I have managed or supported patients with PKU either through pregnancy or through preconception and then pregnancy and had contacts with women via NSPKU work (>40 women; none have ever accessed sapropterin). Most women have reported poor control during their pregnancy – frequently in the first trimester. The first trimester is fraught with difficult to manage sickness, needing to eat as low as 3g protein daily; changing medications to suit the symptoms, and bloodspot testing three times a week (latter ongoing for full pregnancy). The current policy to access sapropterin is ineffective and dangerous – in particular it means sapropterin unlikely to be successfully given to patients quickly enough/early enough in pregnancy to help avoid poor outcomes in offspring.	Comments noted. The committee considered these responses and comments made at the committee meeting, and the guidance document has been updated. Sapropterin is recommended as an option for treating hyperphenylalaninaemia that responds to sapropterin in people with phenylketonuria (PKU), only if they are pregnant (from a positive pregnancy test until birth). See section 1.1 of the FAD. See also sections 3.3, 3.6, 3.19, 3.20, 3.24, 3.31, 3.37 of the FAD.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		Strict metabolic control before and throughout pregnancy reduces foetal risk if dietary control is achieved before conception and maintained throughout pregnancy. The European Guidelines state that treatment should commence pre-conception for maternal PKU, and it emphasises that significant effort should be undertaken to avoid any unplanned pregnancies. The data that is available suggests that current management of females with PKU results in misery for many young women, girls and older women. In the peer reviewed publication from the NSPKU survey 73% of women (n= 300) expressed concerns, fears and distress about pregnancy. 60% were concerned about harm they may cause to a baby, 54% had anxiety about their ability to maintain blood Phe within target, and 48% feared unplanned pregnancy. Some were concerned that it may be unsafe to have a baby as a woman with PKU (39%, n=107); some worried about their parenting skills (16%, n=43), and women even described how they avoided sexual relations. 8% of women were too embarrassed to discuss pregnancy in clinic; 9% said they had a pregnancy termination due to PKU, 14% had a miscarriage and 8% had more than one miscarriage. In the post-natal period, of 93 women, 48% had low mood or sadness, 41% were depressed, 25% felt unable to cope, 33% said they could not care for their PKU as well as their baby, 14% (struggled with childcare needs and 4% worried they might hurt themselves or their baby. 14% thought that child health or developmental problems were linked to PKU. UK pregnancy outcome data is poor and it is not relevant to attempt to compare it with pregnancy data elsewhere. Published data on UK pregnancies include Jovanovic et al 2011 reported on 42 women of reproductive age with PKU and of the 20 pregnancies, only 9 had healthy outcomes. Adams et al (2017) reported on pregnancies in 17 women in Glasgow, 4 out of 17 had offspring with congenital abnormalities. Other data (Maillot et al 2008 and Lee 2005) showed that there is significant negative impacts on offspring IQ and other important markers, relating to blood phe control and whether the mothers were on a preconception diet or started PKU diet after conception. Although this data is 13 years old there is no reason to believe that any improvements in outcome have been realised by the IMD clinical teams caring for women with PKU in the UK. For instance, the rate of planned vs unplanned pregnancies and on diet vs off diet is unlikely to have changed. One London centre for IMD in adults reported on diet status at conception – Cook et al 2018 and 10 of the 22 pregnancies were conceived outside of the desired pregnancy range of phe control; in another large centre in the UK, between 2010 & 2017 an average of 54% of patients conceived offspring outside of the target range of phe. Thus the instigation of tight metabolic control for pregnancy (<300muol/l) is starting too late for the optimal outcomes in these unplanned pregnancies and the current sapropterin policy for access after poor metabolic control is demonstrated in pregnancy fails to prevent foetal exposure to the highly teratogenic effects of phenylalanine. Ford et al 2018 also showed women stopped dietary management shortly after childbirth. They could not cope with the pressures of strict dietary management and caring for their baby (also evidenced in Cook et al 2018). Many described anxiety, depression, tiredness and inability to focus	

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		well after the birth of the baby and some described how they struggled with day-to-day childcare. Postpartum depression in the general population is known to adversely affect infant caregiving activities such as breast feeding and sleep routines (Field et al 2010); there remains a high probability that postnatal depression may be exacerbated by higher blood Phe concentrations. It has been shown that women who remain on treatment post pregnancy are likely to have fewer mental health issues and are better able to cope with parenting (Rohr et al 2004) which in turn, has an important impact on the cognitive outcome of their children. Furthermore, women needed guidance about their own nutritional needs during breastfeeding whilst on the PKU diet post birth. All evidence points to ongoing poor reproductive outcomes for women with PKU in the UK and their offspring - needing interventions ranging from cardiac surgery to statements of special educational needs throughout the education of the offspring (and reduced life chances). Of note, some women with milder forms of PKU (who would be more likely to be sapropterin responders) have not ever done the diet themselves yet have to learn this diet regimen very intensively for preconception and pregnancy purposes. Of note – there is a major health campaign around improving outcomes via influencing the first 1,000 days of life, recognising how important they are for the child's health and development in later life. The window of time preconceptually, post conception and pre birth can determine health outcomes for the whole of adult life. Maternal health is vital to the outcomes of children, especially in their early years. Mothers should be supported during pre-conception, the antenatal period, labour and birth, and the post-natal period. The benefits of using sapropterin would be to make tight metabolic control in the preconception period feasible for many more women that dietary control does now; sapropterin given throughout pregnancy would reduce the difficulties seen in achieving control in the first trimester of pregnancy and post delivery, sapropterin would allow for best cognition and mental health of the mother in the crucial first weeks of motherhood. There should be parity surrounding outcomes in children born to women with PKU and children born with PKU and NICE's sapropterin recommendation is failing on this. *[Case study A received but not reproduced in this table]* *[References received but not reproduced in this table]*	
61	National Society for Phenylketonuria and Metabolic Specialist Dietitian at North Bristol NHS	The committee understood that some people may have greater difficulty adhering to conventional dietary management of PKU and are at higher risk of being unable to control their phenylalanine. Some people may also have difficulty accessing healthcare services. NICE has not mentioned late treated or untreated patients with PKU at any stage; these patients are characterised by learning difficulties, challenging behaviours and also epilepsy.	Comments noted. The committee considered the responses to the ACD on this theme and the comments made at the committee meeting. Section 3.6 of the FAD discusses this issue. The risk of irreversible brain damage reduces with age,

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
	Trust	Data shows that patients with learning difficulties have reduced challenging behaviours when they keep their blood phenylalanine controlled and a number of clinical studies advocate phe restricted diet in adults with late diagnosed or previously untreated PKU due to improvements in subjective measures of alertness, mood, irritability, concentration, destructive behaviour, quality of life and adaptive behaviour (Murphy et al 2005; Fitzgerald et al 2000; Koch et al 1999; Baumeister et al 1998; Pavone et al 1993). Patients experience less anxiety and have fewer behavioural interventions, restraints etc when on a PKU diet (Lee et al 2009). This is clearly beneficial to achieve good metabolic control for patients, and the benefits can be felt by patients and carers alike and is cost effective compared to staffing numbers needed to care for people with challenging behaviours. The diet cannot be easily administered to all of these patients in care homes. There late treated patients with PKU in England, are in care homes and some are being cared for by elderly and vulnerable parents or siblings. These patients have more than one protected characteristic under the Equality Act 2010 and should not be forgotten. *[Case study P received but not reproduced in this table]* *[References received but not reproduced in this table]*	particularly after brain development is complete. So the adverse effects of being unable to follow the protein-restricted diet are considerably reduced in adults compared with the risks in childhood. Adults may still gain considerable benefit from sapropterin because of fewer symptoms related to raised phenylalanine levels, without having to follow the protein-restricted diet as strictly. However, these benefits are included in the economic modelling. Also, in adults the weight-based dose together with the higher average mg/kg dose results in costs that are considerably higher than in children, but the benefits are not correspondingly higher for adults. Even taking into account any uncaptured benefits in adults, the cost-effectiveness estimates are substantially higher than what NICE considers an acceptable use of NHS resources. So, it is not recommended for adults aged over 21. See sections 3.1, 3.2, 3.6, 3.13, 3.23, 3.29, 3.30, 3.34, 3.35, 3.36 and 3.38 of the FAD.
62	National Society for Phenylketonuria and Metabolic Specialist Dietitian at North Bristol NHS Trust	There is clearly much more published data that shows PKU in adulthood to be burdensome, symptomatic and difficult to treat with the PKU diet – I will not cite it all here. In my role at NSPKU I answer the helpline so I am aware of various patient experiences and clinical situation. The below patient gave me permission to share this which illustrates the statistics shown in NSPKU surveys about access to prescribed treatment items in the UK: A Case Study about experiences of adults in the UK system and abroad: *[Case study C received but not reproduced in this table]*	Comments noted. The committee considered the responses to the ACD on this theme and the comments made at the committee meeting. The risk of irreversible brain damage reduces with age, particularly after brain development is complete. So the adverse effects of being unable to follow the protein-restricted diet are considerably reduced in adults compared with the risks in childhood. Adults may still gain considerable benefit from sapropterin because of fewer symptoms related to raised phenylalanine levels, without having to follow the protein-restricted diet as strictly. However, these benefits are included in the economic modelling. Also, in adults the weight-based dose together with the higher average mg/kg dose results in costs that are considerably higher than in children, but the benefits are not correspondingly higher for adults. Even taking into account any uncaptured benefits in adults, the cost-effectiveness estimates are substantially higher than what NICE considers an acceptable use of NHS resources. So, it is not recommended for adults aged over 21. See sections 3.1, 3.2, 3.6, 3.13, 3.23, 3.29, 3.30, 3.34, 3.35, 3.36 and 3.38 of the FAD.
63	British Dietetic Association National Society for	WHY SAPROPTERIN SHOULD NOT BE STOPPED AT THE AGE OF 18 YEARS The draft proposal to stop sapropterin at the age of 18 years is not in the best interests of patients with PKU and I cannot support this. This proposal contradicts the recommendations of the PKU	Comments noted. The committee considered these responses and comments made during the committee meeting, and the guidance document has been updated. See section 1.1 of the FAD

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
	Phenylketonuria	European Guidelines 2017, the USA PKU guidelines and the PKU MRC 1993 group guidelines that treatment should be for life in PKU. By giving this recommendation, NICE is giving an overwhelming message that treatment does not matter in adulthood. It is irrational to relax protein intake in childhood, only to restrict it later in adulthood. It is expected that the proposed recommendation of NICE will lower patient motivation at the age of 18 years; it could also lead to patients failing to attend their metabolic clinics as they consider they are not being offered a realistic or workable treatment option. The dietary treatment for PKU is particularly arduous, unpalatable and consists of a limited range of foods. Many of the foods that are permitted are high in sugar and are discouraged for the general population as they are unhealthy. We currently have no option but to advise these foods as part of a low phenylalanine diet in PKU. See Table 1 for the list of low protein/exchange free foods that are allowed without measurement. Although the dietary difficulties have already been described to NICE, it is necessary to re-explain the gruelling nature of the dietary treatment and the daily struggles faced by patients. It is harsh and unrealistic to expect any individual with PKU to resume such a difficult, unappetizing and complex diet when research and experience repeatedly shows that many patients are unable to restart dietary treatment once it has stopped or been substantially relaxed (see section 'why a dietary treatment only option is inadequate for adults with PKU'). There is overwhelming evidence to demonstrate that most patients are unable to sustain long term dietary treatment (Table 2) and that blood phenylalanine levels increase with age (Medford et al 2017). It is highly likely that stopping sapropterin at the age of 18 years will lead to cessation of treatment. Many young children with PKU develop rigid eating patterns. They are food neophobic and are frightened to try new foods; this is commonly seen from early childhood (Evans et al 2015, MacDonald et al 1997). I have experience of caring for at least 15 children on sapropterin (either on clinical trials or funded by IFR's). We work with children to gradually expand their diet to include a wider range of nutritious foods; this may take many months or even years to accomplish but it is worthwhile when children develop a healthier eating pattern. Thereby, at the age of 18 years, it is unthinkable that patients are expected to return to an abnormal eating patterns they followed in early childhood prior to sapropterin therapy. They will have acquired a taste for higher protein foods. Some of the children in our clinic have been on sapropterin for 9 years; many eat higher protein foods including meat or fish daily. They will also eat regular bread and pasta. They do not use low protein special foods. They take minimal protein substitute. Therefore, they are unlikely to tolerate a low phenylalanine diet again at a later age. It also appears that the age of 18 years is an arbitrary cut off point. Eighteen years is a difficult developmental age when physical growth stops but brain function continues to develop. The brain is still maturing, and strengths and vulnerabilities continue to emerge. It is a time of life when little is normative. It is a period of frequent change that covers many aspects of life: including hospital transition, leaving school, living independently, going to work or University. It is a time when individuals face significant challenges and are expected to assume new responsibilities and obligations.	The committee recognised that stopping treatment and relying on diet alone at 18 years old is not ideal. It would benefit young adults if treatment with sapropterin could be continued for as long as possible during final brain development and transition into adulthood. The maximum age at which sapropterin can be considered a cost-effective use of NHS resources is 21. However, for this to be cost effective people would need to continue the dose they were having when they were under 18. In practice this may mean that some young adults may need more dietary control alongside sapropterin between the ages of 18 and 21 than they would with a higher dose. See sections 3.6, 3.30, 3.34, 3.36 and 3.38 of the FAD.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		Generally, the process of becoming an adult is more gradual and varied today than in the past. Young people take longer to achieve economic and psychological autonomy and early adulthood experiences vary greatly by gender, race and ethnicity, and social class. Many may struggle to find a path to employment, economic security, and well-being. It is important that young adults with PKU try to maintain optimal metabolic control to help them fully utilise any opportunities they are given throughout this process. Adults with PKU who have showed much academic potential as teenagers describe dropping out of University because they have been unable to adhere to their only treatment option of dietary management with consequential result of loss of metabolic control which then impacts on executive function and mental health. Early adulthood is generally a time of heightened psychological vulnerability and onset of serious mental health disorders, with higher rates of psychological distress; problems compounded by failure to recognize illness or to seek treatment. Suddenly exposing patients with PKU to higher phenylalanine levels at the age of 18 years, may increase the risk of mental health issues. It may lead to mood instability, impulsivity, recklessness, and anger. Young adults may participate in risk taking behaviour and young women with PKU may be more vulnerable to maternal PKU syndrome due to unprotected sexual activity. In addition, marginalized young adults, such as those leaving foster care, those with low IQ and autism, and children of low-income immigrant families, are less likely to experience a successful transition to adulthood, and will be particularly vulnerable if sapropterin is stopped. Thereby, the age of 18 years is a critical window of development. It is important that PKU care is not mismanaged at this age. Success or failure in navigating life's paths can set young adults on a course that will strongly affect the future outcome of their adult lives. Allowing patients to continue sapropterin will improve their lives; it will enable them to be independent and enter into the workforce with continued productivity. Stopping sapropterin when people with PKU are in full time education is not appropriate. This is setting people up to fail university education and will cause long term harm and potential financial instability. The decision to offer dietary treatment only from the age of 18 years will magnify inequality, with lasting effects throughout adulthood, with potential impact on morbidity inequalities in later adulthood. Furthermore, by stopping sapropterin, patients will require intensive dietary education at the age of 18 years. They will need considerable re-education with a new clinical team of adult specialists that has not had time to establish trust and rapport with their patients. This will have financial implications that has not been calculated in the cost model. *[References received but not reproduced in this table]* *[Table 1 received but not reproduced in this table]*	
64	British Dietetic Association National Society for Phenylketonuria	Other evidence WHY A DIETARY TREATMENT ONLY OPTION IS INADEQUATE FOR ADULTS WITH PKU AND WHY THEY SHOULD HAVE EQUAL ACCESS TO ALTERNATVE TREATMENT OPTIONS By stopping sapropterin in early adulthood, in the 20 to 30% of patients who are BH4 responsive,	Comments noted. The committee considered the responses to the ACD on this theme and the comments made at the committee meeting. The risk of irreversible brain damage reduces with age, particularly after brain development is complete. So the

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		NICE are leaving this group of patients without a sustainable treatment option in adult life. • It is well established that many adult patients are unable to adhere to long term dietary management. Adherence with the PKU diet becomes increasingly challenging as patients' age, especially as patients transition from adolescence to adulthood. There is plenty of data to show that a high proportion of adult patients are unable to maintain blood phenylalanine levels within target range on dietary management only (not just the 20-30% that NICE suggest in their report). (see Table 2 for evidence). Metabolic control in PKU worsens with age. Equally evidence from other chronic conditions (diabetes, hypertension) shows low patient adherence rates with special diets only but a combination of treatment strategies is a more successful policy. It is also widely accepted that in many other disorders that adherence to special diets is one of the most difficult aspects of treatment, particularly when diet therapy is initiated in adulthood. *[References received but not reproduced in this table]* *[Table 2 and the associated references received but not reproduced in this table]* Ford et al in 2018 from a survey that reported the experiences of over 300 adults with PKU, said that many described their dietary management as complex and impractical and so abandoned treatment, with some withdrawing from medical care [Ford et al 2018]. Some said that the thought of diet recommencement was almost inconceivable. Some adults who remained on diet but maintained higher blood phenylalanine levels than target ranges had lifelong feelings of self-failure. Adults who received support from partners or family coped better with dietary treatment. Reinstitution of diet after relaxation has long been recognised to be problematic (Schuett et al 1985). Many adults have difficultly re-establishing dietary control after a period off diet. In a Polish study, only 29/53 adults managed to return to a low phenylalanine diet for 3 months, and 10 completed a 9-month study protocol [Bik-Multanowski et al 2008]. Patients generally do better only if they have a good support network, perceive that their symptoms improve with treatment, and experience that their dietary treatment is manageable [Finkelson et al 2001]. Many adults try repeatedly to recommence dietary treatment but struggle to sustain it beyond a few weeks. Once they are on diet, if they transiently falter from their strict routine, patients lose motivation and capacity to cope with the demands of dietary treatment and are unable to continue. Patients have a constant sense of failure. The following are some of the unreported survey quotes about returning to dietary treatment from the Living with PKU survey conducted by the NSPKU in 2018. 'My diet was relaxed at 13yrs and then stopped. I came off diet until preconception diet at 30yrs. I enjoy food and eating socially, it's very hard to restrict protein once you've eaten a normal diet for so many years. I have tried to return to diet numerous times, I struggle with the planning and organisation and the time it takes, and also the restriction. I wish I had never been allowed to come off diet. I am off diet'. 'To be good at the diet you need full support from home and medical. If one part is missing, you fall	adverse effects of being unable to follow the protein-restricted diet are considerably reduced in adults compared with the risks in childhood. Adults may still gain considerable benefit from sapropterin because of fewer symptoms related to raised phenylalanine levels, without having to follow the protein-restricted diet as strictly. However, these benefits are included in the economic modelling. Also, in adults the weight-based dose together with the higher average mg/kg dose results in costs that are considerably higher than in children, but the benefits are not correspondingly higher for adults. Even taking into account any uncaptured benefits in adults, the cost-effectiveness estimates are substantially higher than what NICE considers an acceptable use of NHS resources. So, it is not recommended for adults aged over 21. See sections 3.1, 3.2, 3.6, 3.13, 3.23, 3.29, 3.30, 3.34, 3.35, 3.36 and 3.38 of the FAD.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		off the wagon. Then due to the effects of high Phe levels (bad concentration, lethargy, low self-confidence and anxiety) it is IMPOSSIBLE to claw yourself back. It's a cycle of failure and depression'. 'I have difficulty planning tasks, partly due to my PKU, and find it difficult to plan a diet or remember to take formula. I find normal life hard and overwhelming in itself without strict diet and formulas to think about, due to my severe anxiety and depression'. 'Difficult with a husband working long hours and 4 children, tired, bored, socially difficult. Lack enthusiasm for the food choices and suffer with hunger pangs'. Overall, non-adherent patients report more emotional issues related to PKU [Borghi et al 2020]. Patients receiving BH4 report lower practical and emotional impacts because of lower burden of care associated with the diet [Bosch et al 2015]. *[References received but not reproduced in this table]* There are many barriers to long term dietary adherence in PKU and it is it is associated with a high burden of care. These issues have been well described in the literature and are described in Table 3. Treatment burden increases with co-morbidities such as cognitive and mental health issues. In childhood, these burdens are carried by parents/carers. But some adult patients are overwhelmed with the complexity of self-managing their special diet and are unable to effectively sustain this long term, which then negatively affects their wellbeing and outcome. Treatment burden is not assessed within metabolic clinics, but it is important in determining patient capacity to adhere to this treatment regimen. In addition, some adult patients with PKU have low nutrition literacy which further disadvantages their ability to adhere to a low phenylalanine diet. Nutrition literacy is defined as "the degree to which individuals have the capacity to obtain, process, and understand nutrition information and skills needed in order to make appropriate nutrition decisions" [Silk et al 2008] and is a known predictor of dietary adherence [Taylor et al 2018]. Nutrition literacy predicts adherence to healthy/unhealthy diet patterns in adults with a nutrition-related chronic condition. In adults with PKU, limited health literacy is common and disproportionately affects minority populations, older adults with PKU, patients with lower educational attainment and lower incomes. *[References received but not reproduced in this table]* *[Table 3 received but not reproduced in this table]*	
65	British Dietetic Association National Society for Phenylketonuria	EVIDENCE FOR THE NEED FOR LIFELONG CARE IN PKU AND CHRONIC ISSUES EXERIENCED BY ADULTS WITH PKU The main goal of management in PKU is the long-term protection of neurocognitive and psychological functions. For years after the start of newborn screening (in the 1960's), there was controversy over the length of time treatment was necessary. Today, however, there is an abundance of data showing that blood phenylalanine levels maintained within target range are crucial for healthy brain and neuropsychological functioning throughout life.	Comments noted. The committee considered the responses to the ACD on this theme and the comments made at the committee meeting. The risk of irreversible brain damage reduces with age, particularly after brain development is complete. So the adverse effects of being unable to follow the protein-restricted diet are considerably reduced in adults compared with the risks in childhood. Adults may still gain considerable benefit

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		Adults with PKU experience many chronic issues (depression, anxiety, low mood, poor executive function), indicating the ongoing negative effects of high blood phenylalanine levels on the brain and psychological functioning in adulthood. There is almost universal consensus among clinicians that "treatment for life" is the best approach for the early-treated population. Although NICE suggest that dietary treatment is given as the only treatment option, it is clear from the evidence presented that many adults cannot adhere to this. Associated with the absence of practical treatment options is the high rate of patients who are 'lost to follow up' who should attend an adult metabolic clinic. Unfortunately, there is no knowledge about their clinical outcome. It is suggested that around 50% of adult patients with PKU in the UK have been lost to follow up [Burton et al 2005]. A European survey on management of adult patients reported that the majority of patients with PKU in active follow up were aged under 30 years, suggesting that there is a 'lost generation' of older adult patients [Trefz et al 2015]. Even those adult patients who remain in follow up do not have their neurocognitive performance closely monitored and there is no patient registry scrutinising adult clinical outcome in the UK. Trefz et al [Trefz et al 2015] reported that across Europe, only 26 % of health care professionals routinely perform neurocognitive testing in adult patients. Thereby medics, psychiatrists, and psychologists are unlikely to be aware of the full extent of neuropsychiatric comorbidities associated with this disorder. *[References received but not reproduced in this table]* WHAT IS KNOWN ABOUT CLINICAL OUTCOME IN ADULT PATIENTS? • Evidence from a systematic review demonstrates that significant sub-optimal outcomes exist in early treated adults with PKU. High blood phenylalanine levels lead to both acute and chronic neuropsychiatric symptoms. NICE suggest that these symptoms are reversible with dietary treatment, but the evidence clearly shows that the majority of patients with PKU cannot sustain dietary treatment and maintain blood phenylalanine levels below 600 µmol/L, so dietary treatment alone is not adequate to reverse and prevent recurrence of symptoms long term. Patients who have better outcome generally have achieved blood phenylalanine control within treatment guidelines throughout their life. • Impairment in psychiatric, behavioural, and neurocognitive function often reflect the timing, duration, and intensity of phenylalanine exposure. There is wide variability/heterogeneity between individuals. It is unknown if dietary treatment alone can lead to a full remission in psychiatric illness. • Some adults have low IQ due to poor phenylalanine control in childhood – therefore neurological damage is permanent. There is much evidence to suggest that the inability to sustain good metabolic control in childhood is associated with a decline in IQ score and executive function and will have a negative influence in adulthood (Jahja et al. 2017; Koch	from sapropterin because of fewer symptoms related to raised phenylalanine levels, without having to follow the protein-restricted diet as strictly. However, these benefits are included in the economic modelling. Also, in adults the weight-based dose together with the higher average mg/kg dose results in costs that are considerably higher than in children, but the benefits are not correspondingly higher for adults. Even taking into account any uncaptured benefits in adults, the cost-effectiveness estimates are substantially higher than what NICE considers an acceptable use of NHS resources. So, it is not recommended for adults aged over 21. See sections 3.1, 3.2, 3.6, 3.13, 3.23, 3.29, 3.30, 3.34, 3.35, 3.36 and 3.38 of the FAD.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		et al. 2002; Waisbren et al. 1980). For example, Jaha et al 2017 showed that high blood phenylalanine levels in childhood, affect adult cognitive flexibility, executive motor control, executive function in daily life and adult mental health. Weglage (2013) also showed that high blood phenylalanine levels in childhood and adolescence were related to poorer IQ, information processing and attention in adulthood. Lower IQ lessens the patient ability to manage a low phenylalanine diet. Low IQ is linked with social disadvantage (low paid job, living in poverty), which in turn lessens the ability to apply the stringent dietary treatment. *[References received but not reproduced in this table]* • Feldmen et al 2019 showed that older adult patients (> 42 years) with PKU showed poorer information processing and attention compared to young adult patients (< 42 years) and controls. IQ was significantly correlated to blood phenylalanine levels in patients´ childhood and adolescence, and phenylalanine levels had been higher in the adolescent years of older adult patients. *[Reference received but not reproduced in this table]* • Many studies have shown PKU patients had significantly worse test results in memory, problem-solving skills, and strategy (Christ et al. 2010, Jahja et al. 2017, Bartus 2018). There is no evidence to show that this improves with time. *[References received but not reproduced in this table]* • There are a small but increasing number of case reports in recent years that provide evidence that some adult PKU patients develop severe neurological symptoms in later adulthood (see the first part of Table 4- for information about case studies in the literature). Some of these cases are from the UK. They demonstrate that severe decline in neurological function occurs despite relatively normal function for a substantial period. They demonstrate the vulnerability of the brain to high phenylalanine levels. It is possible that there are many similar cases, but they remain unreported by clinics. Not all symptoms have reversed on dietary treatment. Also, authors generally do not report the longer-term outcome of these cases. *[References received but not reproduced in this table]* • There is widespread white matter compromise in individuals with PKU, which is exacerbated by increasing age. Hawks Z, Hood AM, Lerman-Sinkoff DB, Shimony JS, Rutlin J, Lagoni D, Grange DK, White DA. White and gray matter brain development in children and young adults with phenylketonuria. Neuroimage Clin. 2019;23:101916 • It has been observed that serotonin and to a lesser extent dopamine metabolites are reduced in adult PKU patients and correlate with specific gray matter atrophy patterns.	

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		[Reference received but not reproduced in this table] • A range of anxiety disorders, including generalized anxiety, panic disorder, specific phobias, and obsessive-compulsive disorder have been reported in PKU and have been associated with low serotonin in the brain in adults with PKU. Rates of depression are considered higher in adults with PKU than the general population. Recent data from the adult PKU clinic in Manchester showed that approximately 75% of the clinic population (n=244) had a 2-year average blood phenylalanine level of >600 µmol/l and this group were more likely to have a diagnosis of low mood, depression, anxiety or mood swings, but only low mood reached statistical significance ($p < 0.05$). They suggested that many adult PKU patients may be lost to follow up, and therefore may be receiving treatment for mental health conditions in the community. Ford et al 2018, reported that in >300 adult patients with PKU from the UK, that 40%, (n=131/331) used antidepressants and 18% (n=60/334) used anxiolytics. *[References received but not reproduced in this table]* • Table 4 demonstrates the recent wealth of studies and care reports that have reported on clinical outcome in adult patients with PKU *[Table 4 and the associated references received but not reproduced in this table]*	
66	British Dietetic Association National Society for Phenylketonuria	UNTREATED ADULTS WITH PKU AND INEQUALITY OF ACCESS TO TREATMENT Previously untreated adults with PKU should also be considered for sapropterin treatment. There are many late diagnosed and untreated patients with PKU who were either born prior to newborn screening, failed newborn screening in the 1960's or have immigrated from countries without newborn screening or treatment. Untreated patients with severe intellectual disability and challenging behavioural problems have high support needs, and some may live in social care homes or with very elderly relatives. Interventions to lower blood phenylalanine levels may be beneficial. There is evidence from case studies and cohort studies that dietary treatment may reduce aggressive behaviour, self-injury, hyperactivity, restlessness, irritability, sleep disorders, and anxiety. It improves mood, social interactions, verbal communication, and daily living skills. It also improves attention span, alertness, short-term memory processes, motor skills, seizures, spasticity, and tremors. It will reduce nursing time, use of sedatives, anti-psychotic, anticonvulsants; it will also improve eczema and body odour. Unfortunately, many care homes are unable to cope with dietary treatment due to the time it takes to prepare suitable food and supervise that it is given appropriately. This vulnerable group of patients should be given equal opportunity to see if they are sapropterin responders as this treatment could improve their quality of life considerably without the need for strict dietary treatment. It will also ease the burden of care on health and care services. *[References received but not reproduced in this table]*	Comments noted. The committee considered responses received on this issue and comments made at the committee meeting, and the guidance document has been updated. Adults may still gain considerable benefit from sapropterin because of fewer symptoms related to raised phenylalanine levels, without having to follow the protein-restricted diet as strictly. However, these benefits are included in the economic modelling. Also, in adults the weight-based dose together with the higher average mg/kg dose results in costs that are considerably higher than in children, but the benefits are not correspondingly higher for adults. Even taking into account any uncaptured benefits in adults, the cost-effectiveness estimates are substantially higher than what NICE considers an acceptable use of NHS resources. So, it is not recommended for adults aged over 21. See sections 3.1, 3.2, 3.6, 3.13, 3.23, 3.29, 3.30, 3.34, 3.35, 3.36 and 3.38 of the FAD
67	British Dietetic Association	MATERNAL PKU AND EVIDENCE TO SUPPORT THE NEED FOR SAPROPTERIN DURING PRE-CONCEPTION AND POST NATALLY	Comments noted. The committee considered these responses and comments made at the committee meeting,

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
	National Society for Phenylketonuria	• Achieving a healthy pregnancy outcome in women with PKU is strongly influenced by their blood phenylalanine control throughout pregnancy as well as their health status and diet. • High blood phenylalanine levels during pregnancy have a teratogenic effect on the developing foetus that causes growth retardation, microcephaly, intellectual disabilities, and birth defects, including congenital heart defects (CHD). A summary of reported effects of poor blood phenylalanine control in maternal PKU is given in table 5. Generally, the longer blood phenylalanine levels are out of metabolic control, the worse the foetal outcome. Control of maternal blood phenylalanine during pregnancy prevents most if not all of these complications (Lenke and Levy 1980; Rohr et al. 1987; Koch et al. 2003). Children born to mothers with PKU who attain satisfactory blood phenylalanine control before pregnancy are comparable to the normal population. • It is recommended that woman with PKU should follow a strict low phenylalanine diet prior to pregnancy/pre-conception as features of maternal PKU syndrome are preventable by starting a low phenylalanine diet before conception. The time to reach stable and acceptable blood phenylalanine concentrations varies between women. It is influenced by personal conditions (organizational skills, IQ, work conditions) and family support, which will affect the ability to adhere to strict long-term diet. • Evidence has proven that sapropterin lowers blood phenylalanine in BH4 responsive patients with PKU. Thereby, there is no reason why it should not lower blood phenylalanine levels during the pre-conception period and pregnancy in BH4 responsive women (see later discussion). • About half of pregnancies in maternal PKU in the UK are accidental. This is similar to national figures for non PKU pregnancy. This means at the time of conception; maternal blood phenylalanine levels are likely to be higher than target ranges. Furthermore, some women may delay seeking advice once they know they are pregnant due to fear and guilt leading to further delay before stringent diet therapy is commenced. Young women, those with lower education and living on income support are the most vulnerable and are more likely to experience accidental pregnancy. Furthermore, women with disability are less likely to use reliable contraception and are particularly at risk (Holdsworth et al 2018). *[Reference received but not reproduced in this table]* • Maternal delay in attainment of acceptable blood phenylalanine control is associated with decline in their child's developmental outcome/IQ score. Waisbren and Azen (2003) conducted a prospective longitudinal study that assessed cognitive and behavioural outcomes in children from women with PKU. Two hundred and twenty-eight children who were born to mothers with treated PKU or untreated mild hyperphenylalaninemia were compared with 70 control subjects at 7 years of age. They found that the children's cognitive outcome negatively correlated with the number of gestational weeks that elapsed until maternal metabolic control was achieved. There was an increased risk of low	and the guidance document has been updated. Sapropterin is recommended as an option for treating hyperphenylalaninaemia that responds to sapropterin in people with phenylketonuria (PKU), only if they are pregnant (from a positive pregnancy test until birth). Section 1.1 of the FAD. See also sections 3.3, 3.6, 3.19, 3.20, 3.24, 3.31, 3.37 of the FAD.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		IQ in the children if the mother came from a lower socio-economic background and was also unable to provide a stimulating early home environment. The postnatal environment also significantly affected outcome. *[Reference received but not reproduced in this table]* • In a separate study, Waisbren followed up 57 children from 24 mothers with PKU. The children ranged in age from 1 month to 26 years with 21 (62%) over 6 years. The mean IQ of children was 94, with 12% performing in the range of intellectual disability (IQ < 70). Among children >5 years of age, 25% had learning disabilities, 31% had attention deficit hyperactivity disorder (ADHD), 22% were on ADHD medication, and 34% had a diagnosis of anxiety and/or depression. *[Reference received but not reproduced in this table]* • Widaman demonstrated a threshold effect of a mother's mean blood phenylalanine of 400 µmol/l in relationship to their child's IQ. With every further increase of 60 µmol/l Phe, the IQ decreased by 4.7 points in their infant. *[Reference received but not reproduced in this table]* • In the UK, there is no current registry describing child/foetal outcome following maternal PKU pregnancy. However, in 2008, Maillot et al conducted a retrospective review of outcomes in 105 children born to mothers with PKU in the UK. They found that IQ and developmental quotient (DQ) at age 1 and age 8 were higher in children whose mothers started a low phenylalanine diet before pregnancy compared with those whose mothers started the diet after pregnancy began, at a mean gestational age of 10 weeks. Starting the diet before the beginning of pregnancy also reduced the risk of CHD (0% for the prior-to-pregnancy diet group vs. 12.5% for the group initiating diet 10 weeks after pregnancy began). Maillot F, Lilburn M, Baudin J, Morley DW, Lee PJ. Factors influencing outcomes in the offspring of mothers with phenylketonuria during pregnancy: the importance of variation in maternal blood phenylalanine. Am J Clin Nutr. 2008 Sep;88(3):700-5. There is also evidence of other poor outcome of maternal PKU in the UK (see Table 5 for maternal PKU studies describing outcome). • Poor maternal nutrition in pregnancy is also associated with worse outcome. Congenital heart disease is higher when women are eating a poor quality diet particularly if they consume a low protein, low fat and low vitamin B12 intake. The use of sapropterin will increase the intake of these nutrients in BH4 responsive women. *[Reference received but not reproduced in this table]* • Most women with maternal PKU find a strict low phenylalanine diet particularly difficult in the pre-conception period. Some women even chose not to have children due to concern and fear about their ability to cope with pregnancy. *[Reference received but not reproduced in this table]* • Data from case studies (Table 5) suggests that sapropterin is safe in pregnancy and will lower blood phenylalanine concentrations in sapropterin responsive women. Prescription of sapropterin to responsive women in the pre-conception period may lessen the time	

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		required to achieve acceptable blood phenylalanine control prior to pregnancy. It should help improve nutritional status. During pregnancy it should enable women to eat more natural protein so they are less reliant on artificial nutrition; this should improve the quality of blood nutrient supply available to the infant. In addition, administration of sapropterin in combination with dietary treatment in the post-natal period may help women maintain blood phenylalanine control within acceptable limits, assist women to sustain breast feeding by helping them eat sufficient calories, and lessen any PKU related symptoms due to poor metabolic control. • There is a current NHS policy that suggests that sapropterin can be prescribed only when women demonstrate they are unable to achieve lower blood phenylalanine levels in pregnancy. At this point women may be several weeks pregnant and no prior BH4 responsive test will have been conducted. This policy is only allowing sapropterin to be being used as a type of 'rescue therapy' when the clinical situation is particularly difficult and BH4 responsiveness has not been proven. This is inappropriate and this practice will not demonstrate the full benefit of sapropterin. BH4 responsive women will gain most benefit from sapropterin if it is used during the preconception phase enabling them to cope better with their diet therapy as previously explained. • Sapropterin also has a role to place post pregnancy. Sapropterin given with a relaxed low phenylalanine diet post pregnancy, may lead to improved maternal mood and ability to cope with parenting leading to better outcome in children. Many women are unable to sustain dietary treatment post pregnancy as they consider a low phenylalanine diet too challenging when caring for their infant. In Waisbren's follow up study of maternal PKU pregnancies, their school aged children were more likely to exhibit learning disabilities, ADHD, or emotional and behavioural disturbances. Their mothers with PKU were more likely to be depressed or anxious. The authors suggested that the environmental circumstances, including the home environment, maternal depression and anxiety contributed to the issues seen. In Waisbren's study although many women perceived themselves as functioning well in their daily life, 25% performed in the borderline intellectual range. *[Reference received but not reproduced in this table]* *[Table 5 and the associated references received but not reproduced in this table]*	
68	British Dietetic Association National Society for Phenylketonuria	COST EFFECTIVENESS MODEL The following costs do not appear to have been factored in the cost of model used by NICE: Health care costs • Cost of any medications such as anti-depressants, ADHD medications, laxatives with diet treated patients with PKU. • Cost of medical care of co-morbidities – particularly costs of psychiatric, psychology or counselling costs. • Increased dietetic and health professional costs associated with extra time necessary for counselling when poor metabolic control occurs in patients with PKU.	Comments noted. The committee considered these responses and comments made at the committee meeting, and the guidance document has been updated. See sections 3.13, 3.23, 3.24 of the FAD.

No.	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		• Costs of maternal PKU (costs of obstetric care, foetal scans, anti-vomiting medications, maternal hospital admissions, infant cardiac care). • Costs of nursing time in late treated patients with PKU in care homes. Community costs • Cost of GP visits • Cost of social services involvement with poor blood phenylalanine. • Cost of additional education in schools or university. • Costs of extra educational needs of children of women with poorly controlled maternal PKU Patient costs • Loss of earnings through time spent managing the diet. Society costs • Loss of work productivity	
79	British Dietetic Association National Society for Phenylketonuria	DOSE OF SAPROPTERIN The dose of sapropterin should be an average of 10 mg/kg as patients may need from 5 to 20 mg/kg. Although a maximum dose of 0 mg/kg will be satisfactory for many, there should be the ability to prescribe to a maximum of 20 mg/kg in the patients who benefit from this.	Comments noted. The committee considered these responses and comments made during the committee meeting, and the guidance document has been updated. The dose for children can be increased above the starting dose of 10 mg/kg, only if target blood phenylalanine levels are not achieved at a dose of 10 mg/kg. So, it is recommended for treating PKU in people under 18, normally at a dose of 10 mg/kg. See sections 1.1, 3.11, 3.21, 3.28, 3.30 of the FAD.

NICE National Institute for Health and Care Excellence

Sapropterin for treating phenylketonuria [ID1475]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 18 March 2021 **email:** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**BioMarin International Limited**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**No past, present direct or indirect link or funding from the tobacco industry**]
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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NICE National Institute for Health and Care Excellence

Sapropterin for treating phenylketonuria [ID1475]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 18 March 2021 **email:** NICE DOCS

1	In regard to the recommendation of sapropterin limited only to phenylketonuria (PKU) patients that are under 18 years of age, BioMarin (the Company) would like to state that all PKU patients, responding to treatment, could benefit from the sapropterin treatment. The health economic model that the company provided, indicates that for patients, below 18 years old, who start treatment and remain for lifetime, sapropterin is a cost-effective treatment in comparison to the standard of care when considering NICE's cost effectiveness thresholds. This finding is further confirmed in the new decision tree model that was submitted to the committee. The Company believes that this should be the correct interpretation of the data carried through into the policy.
2	In page 3, the appraisal consultation document states that *"there is no clinical trial or registry evidence to show whether sapropterin reduces the need for a protein-restricted diet or how it affects quality of life"*. The Company would like to state again that there are numerous publications showing that sapropterin treatment contributes to the decrease of the use of protein supplements. A list of relevant references follows in support to the Company's argument: • Yilmaz O, Quintana A, Rossi A, Dam E, Özel H, Rocha J, et al. Use of Special Medical Foods with Sapropterin in PKU, ESPKU conference 2018 (cross sectional survey) • Scala, I., Concolino, D., Casa, R.D. et al. Long-term follow-up of patients with phenylketonuria treated with tetrahydrobiopterin: a seven years' experience. Orphanet J Rare Dis 10, 14 (2015). https://doi.org/10.1186/s13023-015-0227-8 (no-profit open-label interventional trial) • Thiele AG, Weigel JF, Ziesch B, Rohde C, Mütze U, Ceglarek U, Thiery J, Müller AS, Kiess W, Beblo S. Nutritional Changes and Micronutrient Supply in Patients with Phenylketonuria Under Therapy with Tetrahydrobiopterin (BH(4)). JIMD Rep. 2013;9:31-40. doi: 10.1007/8904_2012_176. Epub 2012 Oct 17. PMID: 23430545; PMCID: PMC3565664. (open-label interventional trial) • Singh, R.H., Quirk, M.E., Douglas, T.D. et al. BH4 therapy impacts the nutrition status and intake in children with phenylketonuria: 2-year follow-up. J Inherit Metab Dis 33, 689–695 (2010). https://doi.org/10.1007/s10545-010-9224-1 (open-label interventional trial) • Burlina A, Blau N. Effect of BH(4) supplementation on phenylalanine tolerance. J Inherit Metab Dis. 2009 Feb;32(1):40-5. doi: 10.1007/s10545-008-0947-1. Epub 2008 Dec 9. PMID: 19067227. (retrospective clinical study) Furthermore, the long-term PKU registries, KAMPER in Europe and PKUDOS in the US, also shows that patients receiving sapropterin experience decrease in their blood phenylalanine (Phe) levels while their natural protein intake increases. (Muntau A, Lagler F, Feillet F, Alm J, Burlina A, Belanger-Quintana A, et al. Seventh Interim Analysis of the Kuvan® Adult Maternal Paediatric European Registry (KAMPER): Interim Results in Phenylketonuria Patients. Poster.; 2017, Longo N, Arnold GL, Pridjian G, Enns GM, Ficicioglu C, Parker S, et al. Long-term safety and efficacy of sapropterin: The PKUDOS registry experience. Mol Genet Metab. 2015;114(4):557-63). The above data has been corroborated by a panel of UK clinical experts that supported a minimum of 50% reduction in the use of protein supplements, potentially reaching 100% in highly responsive patients.
3	In page 4, the ACD states that "the dose of sapropterin is based on weight", the Company would like to clarify that it is the total daily dose that is based on weight. The dose per kg for a patient will not be affected if their weight is higher, all patients would remain on the same dose, i.e. 10 mg/kg regardless if they weight 20 or 70 kgs. It is the total daily dose that would increase.
4	In pages 4 and 21, the ACD states that "there is not enough evidence on how sapropterin might be used to prevent harm to the unborn child in women with PKU who are pregnant or trying to conceive" and "avoiding harm to the developing foetus was clearly important, and the committee welcomes

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comments and further evidence on the potential use of sapropterin in women with PKU of childbearing age, or those planning pregnancy, to prevent harm to the unborn child", respectively.

The Company would like to clarify that the number of maternal PKU patients, if they are to be included in the policy, will be small. UK clinical experts estimate that there are approximately 50 to 60 PKU pregnancies per annum in the whole of UK. Of these pregnancies, it is estimated that the number of pregnant patients who will be in clinic and responsive is approximately 10 per annum. These patients might also require sapropterin treatment only for 6 to 9 months. The UK clinical experts have also confirmed that Phe tolerance increases as the foetus grows and starts to metabolise Phe itself which enables mothers to take more natural protein. In comparison to the life-time costs that would be associated with managing a child with PKU Syndrome, offering the option of sapropterin to pregnant PKU patients would result in negligible overall budget impact.

Furthermore, the Company would like to provide further evidence to confirm that sapropterin is associated with the same benefits in terms of reduction in blood Phe levels and increased dietary Phe intake in the maternal PKU population as in the overall PKU population. PKUMOMS, the PKU in the Maternal Phenylketonuria Observational Program is a sub- registry of PKUDOS with two data cuts, in June 2013 and December 2018.

The June 2013 data-cut of the PKU-MOMS sub-registry contained data from 21 pregnancies in women with PKU, five of whom were treated with sapropterin before pregnancy (but not during pregnancy), and 16 of whom were treated with sapropterin during pregnancy. Excluding data for spontaneous abortions (n = 4), the data show that the mean of the median blood Phe levels (204.7, SD: 126.6 µmol/L; n = 14) for women treated with sapropterin during pregnancy was 23% lower and had a 58% smaller standard deviation compared with the blood Phe (267.4, SD: 300.7 µmol/L; n = 3) for women who were not treated with sapropterin during pregnancy (i.e. treated prior to pregnancy group). Women on sapropterin during pregnancy experienced fewer blood Phe values above 360 µmol/L. When median blood Phe concentration was < 360 µmol/L throughout pregnancy, 75% (12/16) of pregnancy outcomes were normal versus 40% (2/5) of pregnancy outcomes when the median blood Phe was > 360 µmol/L.

Grange et al. 2014, publication from PKU-MOMS, clearly shows that sapropterin during pregnancy leads to better Phe control. (Grange 2013)

The December 2018 data-cut of the PKU-MOMS sub-registry included data from ** women reporting ** pregnancies (several patients remained in the study throughout multiple pregnancies) with a mean sapropterin exposure during pregnancy of [redacted] ([redacted]) (BioMarin, data on file). The mean sapropterin dose was [redacted] mg/kg/day prior to pregnancy ([redacted]), [redacted] mg/kg/day during pregnancy ([redacted]), and [redacted] mg/kg/day after pregnancy ([redacted]). Mean blood Phe was [redacted] µmol/L ([redacted]) prior to pregnancy, [redacted] µmol/L ([redacted]) during the 1st trimester, [redacted] µmol/L ([redacted]) during the 2nd trimester, and [redacted] µmol/L ([redacted]) during the 3rd trimester.

The following birth outcome data were available for the December 2018 data-cut (reported as adverse event data):

- Of [redacted] pregnancies which ended in spontaneous abortion, [redacted] had at least one episode of maternal blood Phe > 360 µmol/L recorded during pregnancy.
- [redacted]Of [redacted] pregnancies with birth outcome data available, [redacted] were reported as normal and [redacted] were reported as abnormal. [redacted]

At the January 2017 data-cut of KAMPER, [redacted] women participated in the KAMPER maternal sub-registry, with a total of [redacted] pregnancies being reported ([redacted]). Of the [redacted] pregnancies with available data, all [redacted] resulted in full term live birth deliveries, with all infant conditions

Sapropterin for treating phenylketonuria [ID1475]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 18 March 2021 **email:** NICE DOCS

	at birth reported as normal. At the January 2019 data-cut of KAMPER, data from [redacted] were available. The mean age at delivery was [redacted] ([redacted]) years. The sapropterin dose was constant prior to, during, and after pregnancy, with a median dose of [redacted] mg/kg/day; the mean duration of exposure during pregnancy was [redacted] days ([redacted]). Maternal blood Phe concentrations were either within the clinical range ([redacted]) or high ([redacted]) during the 1st trimester of pregnancy, were within the clinical range (n = [redacted]) during the 2nd trimester, and were either within the clinical range (n = [redacted]) or low (< 120 µmol/L, n = [redacted]) during the 3rd trimester. Furthermore, additional publications including, Feillet 2014 and Nyuzuki 2019 further state that sapropterin use in pregnant woman leads to better blood Phe control and increased Phe tolerance. Feillet 2014 also reported the offspring of the seven pregnancies were all normal babies with normal birth measurements and outcomes. Nyuzuki 2019 reported normal growth and development of the child confirming the efficacy and safety of sapropterin in maternal PKU. International best practice guideline (Muntau 2019), also recommends sapropterin response testing for pregnant woman with PKU.
5	In page 5, the ACD states that "childhood is the most critical period for brain development". The Company would like to state that brain development continues up to the age of 25 (which is also stated in page 6 of the consultation document), thus adolescence and early adulthood are also critical periods for brain development, education and social development. Furthermore, it has been widely demonstrated that adolescence and early adulthood are periods when Phe control becomes problematic.
6	In page 6, the ACD states that "Clinical experts estimated that 10% to 20% of patients struggle to maintain control of blood Phe levels". The Company would like to present data from Walter 2002 publication which show that adherence to a Phe-restricted diet is extremely challenging with as many as 75% of adolescents being unable to keep their blood Phe levels within the recommended target range. (Walter 2002) A similar observation from the US shows that Phe levels increase as age increases. This assessment of current management by Jurecki et al. included PKU clinics across the US in 2015 covering approximately 50% of PKU patients followed in clinics in the US showed that 12% of patients aged 0-4 years old had Phe levels higher than 360 µmol/L, 29% of patients aged 5-12 years old had Phe levels higher than 360 µmol/L and 40% of patients aged 13-17 years old had Phe levels higher than 360 µmol/L.
7	In page 6, the ACD states that "good control of blood Phe levels (below 200 micromols per litre) should be maintained if possible, but there are no strict guidelines or target Phe levels used in clinical practice". However, it is clearly stated in the 2017 EU Guidelines that pregnant PKU patients should maintain their Phe levels between 120 to 360 micromol/L (van Spronsen 2017) and UK clinical experts follow the European PKU guidelines.
8	In pages 17 and 18, the ACD states that "the model time horizon is not long enough to capture long-term brain damage in people with PKU and the model is not appropriate to capture the effects of PKU in pregnancy". The Company would like to state that owing to the teratogenic effects on children born to mothers with PKU, the model included an additional utility gain of [redacted] that sapropterin can potentially bring. This was presented to the Committee in the new decision tree model.
9	In page 19, the ACD states that "the ERG advised that the utility reductions may be double counted, because the reductions were already captured for different PKU symptom states". The Company would like to clarify that utility reductions have not been double counted. The health state vignettes that were presented to the general population in Sweden and clinical experts in England, did not include a description for intellectual disability and IQ deficits, hence inclusion of these in the decision tree model is not double counting.
10	In page 19, the ACD states that "the ERG did acknowledge that increased blood Phe levels can harm

the unborn child, but the extent of lost utility is unclear, as is the effect of sapropterin on that utility loss". The Company will like to recount 2 publications, Lenke et al. 1980 and Koch et al. 2003. High Phe concentration in PKU mothers crosses the placenta by active transport, resulting in 70% to 80% increased foetal concentration of Phe compared with maternal concentration. Elevated Phe is toxic and teratogenic to a developing foetus. Women of child-bearing age with high Phe during and before pregnancy leads to an increased risk of spontaneous miscarriage (24%), intrauterine growth retardation (40%), microcephaly (73%), global developmental delays (92%), and congenital heart defects (12%) in their offspring.

These risk of teratogenic effects in offspring, can be potentially reduced by sapropterin use pre-conception and during pregnancy [Feillet 2014 and Nyuzuki 2019]. The decision tree model used an increase in utility of [redacted] to address this reduced long-term risk of abnormalities to the child.

11

In page 21, the ACD states that "the committee concluded that escalation above the dose of 10 mg/kg for children and 12.5 mg/kg for adults would have a significant effect on the cost effectiveness of the treatment". The Company will like to state that in the ERG model that was presented to the committee, dose escalation from 10 mg/kg to 12.7 mg/kg had limited impact. The results are presented in the table below:

Age	Mean dosage	Mean cost per day	Reduction in daily PRD cost	Incremental daily cost	Annual incremental cost	Symptom severity	QALY incremental gain	ICER per QALY gained
0-3 years	10mg/kg	[redacted]	£20.14	[redacted]	[redacted]	Mild	0.130	[redacted]
		[redacted]	£20.14	[redacted]	[redacted]	Moderate	0.134	[redacted]
		[redacted]	£20.14	[redacted]	[redacted]	Severe	0.145	[redacted]
	12.7mg/kg	[redacted]	£20.14	[redacted]	[redacted]	Mild	0.130	[redacted]
		[redacted]	£20.14	[redacted]	[redacted]	Moderate	0.134	[redacted]
		[redacted]	£20.14	[redacted]	[redacted]	Severe	0.145	[redacted]
0-17 years	10mg/kg	[redacted]	£22.41	[redacted]	[redacted]	Mild	0.130	[redacted]
		[redacted]	£22.41	[redacted]	[redacted]	Moderate	0.134	[redacted]
		[redacted]	£22.41	[redacted]	[redacted]	Severe	0.145	[redacted]
	12.7mg/kg	[redacted]	£22.41	[redacted]	[redacted]	Mild	0.130	[redacted]
		[redacted]	£22.41	[redacted]	[redacted]	Moderate	0.134	[redacted]
		[redacted]	£22.41	[redacted]	[redacted]	Severe	0.145	[redacted]

Furthermore, the new decision tree model submitted by the Company to the committee, the ICERs were:

Subgroups	Mean dosage(mg/kg/day)	Mean cost per day	Reduction in daily PRD cost	Incremental daily cost	Annual incremental cost	Symptom severity level	QALY incremental gain	ICER per QALY gained

Sapropterin for treating phenylketonuria [ID1475]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 18 March 2021 **email:** NICE DOCS

	0-3 years	12.7mg /kg	[redacted]	£0.02	[redacted]	[redacted]	Mild	0.77	[redacted]
			[redacted]	£0.02	[redacted]	[redacted]	Moderate	0.82	[redacted]
			[redacted]	£0.02	[redacted]	[redacted]	Severe	0.88	[redacted]
	0-17 years	12.7mg /kg	[redacted]	£0.02	[redacted]	[redacted]	Mild	0.77	[redacted]
			[redacted]	£0.02	[redacted]	[redacted]	Moderate	0.82	[redacted]
			[redacted]	£0.02	[redacted]	[redacted]	Severe	0.88	[redacted]
	Thus, the dose increase to 12.7 mg/kg has shown limited impact on ICER for <18-year olds.								

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
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- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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Sapropterin for treating phenylketonuria.
Appraisal consultation document

18th March 2021

There are 3 questions that are asked:

1. Has all the relevant evidence been taken into account?
2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
3. Are there any aspects of the recommendations that need particular consideration, to avoid unlawful discrimination?

The document recommendations fall short of fulfilling these questions. On the basis of unlawful discrimination stopping any drug at 18 years of age is detrimental to a person's wellbeing and coercive. This recommendation shows a complete lack and disregard of any understanding towards the treatment of phenylketonuria (PKU). The committee making these recommendations have neglected the relevant evidence for those adults at 18 years or older.

This decision will have a devasting impact on a young person it potentially will ruin their life chances, as sustaining a restricted diet after 18 is not feasible or sustainable and the reasoning made by NICE flawed. There is agreement that sapropterin is clinically appropriate, effective and beneficial for people with PKU that respond to sapropterin; why should this benefit be stopped at 18 years of age when treatment is for life.

There is evidence to refute the statement *'the dose of sapropterin is based on weight so costs are higher for adults than children but there is no extra increase in quality of life to offset these costs.'* Yes, it is true costs are lower for children, but to make a statement that it can be withdrawn as it has not benefit to quality of life (QoL) is short sighted. There is overwhelming evidence to suggest the contrary, irreversible brain damage is avoided for all children if treatment is started on time. However, the pathology for brain dysfunction continues throughout life, with evidence [1] showing higher blood phenylalanine

concentrations are responsible for neurocognitive delay, which impacts on the quality of life. Adults non-compliant to diet therapy have a range of neurological, psychosocial, and physical dysfunctions. This evidence cannot be ignored, dismissed or compared to a price tag.

Has all the relevant evidence been taken into account?

Evidence for poor dietary adherence leading to high blood phenylalanine concentrations and sub optimal neurocognition. (Table 1 and 2)

1. Sapropterin is only available as an adjunctive therapy for 20 to 30 % of the UK PKU population. The majority of patients have no alternative choice. Limiting drug therapy for those with a choice is unfair.
2. Sapropterin as NICE have stated reduces blood phenylalanine concentrations allowing a less restricted diet, and the benefits of lower blood phenylalanine are reducing neurocognitive damage, with evidence showing higher blood phenylalanine concentrations lead to decreased neurocognition
3. Without sapropterin diet therapy is rigorous, restrictive and lifelong. There is compelling evidence that compliance, together with increased phenylalanine concentrations deteriorates with age.
4. Dietary treatment is strict and demanding, mild cognitive abnormalities are recognised from a young age and these affect QoL of patients and families. Bosch et al 2015 [2] describes the treatment of sapropterin compared to dietary treatment alone, with adults being less aggressive and improve cognition, with less social impact and greater dietary freedom.
5. Although the early initiation of dietary treatment prevents the most severe psychiatric and neurological symptoms, especially intellectual disability; behavioural and emotional problems are still described in many continuously treated children and adolescents.
6. The impairment of these mental processes leads to inattention, hyperactivity and impulsiveness in early treated PKU children. Other behaviours have been cited such as anxiety, phobias, depression, social isolation and psychosomatic difficulties.

7. Less adherence to treatment with consequent higher blood phenylalanine concentrations are partially responsible for these neuropsychological symptoms
8. There is evidence to suggest mild intellectual disability (albeit not as severe as untreated PKU subjects) is found in early treated PKU children and continues lifelong.
9. There are several studies all showing behaviour and emotional problems in early treated children and adolescents have been reported (Vieira 2018). Parents report attention problems and hyperactivity with nonadherent to treatment and intellectually low performing patients with PKU.
10. The proposed mechanisms for these impairments include dopamine depletion and white matter pathology. Neuroimaging studies demonstrate high signal intensity in the periventricular while matter observed in PKU patients. Research shows that this pathology is associated with metabolic control and possibly only reversed with a strict low phenylalanine diet [1, 3]
11. Brumm et al [4]shows psychiatric and psychological problems are well documented across the lifespan of early treated PKU patients. Common problems: attention deficient, poor school performance, low achievement motivation, decreased social competence, lower autonomy and self-esteem. Moving into adulthood, despite early treatment these issues continue: low self-esteem, a lack of autonomy, depression, anxiety, phobias, decreased positive emotions, immature social skills and social isolation. The correlation between the level of metabolic control and severity of symptoms suggests a biological basis of psychiatric dysfunction.
12. Although it is difficult to quantify, additional psychosocial factors such as the burden of living with a chronic disorder may contribute to psychological and psychiatric outcome in PKU [5, 6].
13. Treatment is the same for those at all ages and therefore, cannot be discriminated on the basis of age. The practicality of sustaining treatment becomes more difficult and almost impossible for many with PKU. To remove a drug treatment at any age is subjecting this group of patients to a deterioration in neurocognition.

The evidence from studies in table 1 and 2 are overwhelming in their findings

a) dietary adherence decreases over time

b) phenylalanine concentrations deteriorate over time

c) neurological damage is continuous increasing with higher blood phenylalanine concentrations

d) quality of life due to neurological dysfunction is detrimental to the patient and family

Neurological damage is a constant clinical concern, with a proven pathology. This damage increases with poor metabolic control which is more likely in those over the age of 10 years with many adults unable to sustain dietary treatment and the required low blood phenylalanine concentrations within the target therapeutic range.

It would be unethical to withdraw treatment at any age, if it is beneficial. There is a large body of evidence which has been disregarded. To state that the quality of life will not be further enhanced after 18 years of age is factually wrong. In all the other countries using sapropterin, withdrawing treatment, has never been considered a viable or ethical policy. The evidence from NICE shows that those taking sapropterin can achieve target blood phenylalanine concentrations avoiding the consequences of damaging higher blood phenylalanine levels. NICE acknowledge lower IQ scores and neuropsychological impairments are present in PKU patients, therefore, to stop treatment at 18 years would lead inevitably lead to a deterioration in mental wellbeing and quality of living.

To make the statement *there is no risk of long term brain damage in adults* is completely misguided and unsubstantiated, the evidence from Table 1and 2 repeatedly shows nonadherence to diet, becomes harder with age, and the majority of teenagers and adults have phenylalanine concentrations outside the therapeutic range with evidence based research to show brain damage is continuous impacting life choices.

Routine monitoring of emotional and behavioural and psychosocial symptoms in individuals with PKU is necessary together with longitudinal studies to evaluate the

impact of new and emerging therapies. These reported clinical findings have a significant lifelong impact on the quality of life and social status of patients.

On behalf of the British Inherited Metabolic Disease -Dietitians Group, we strongly recommend the evidence is reappraised in the light of peer review publications. Any treatment that can reduce blood phenylalanine concentrations prevents long term brain deterioration, and the associating insidious detriments to daily living.

Yours sincerely

[redacted]

(Chair BIMDG-DG group)

References

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Table 1. Peer review evidence summarising poor dietary adherence and quality of life cognitive impact

Author/Year	Summary of main findings
Feldmann 2019	***Neurocognitive functioning in adults with phenylketonuria: Report of a 10 year follow up*** 35 patients with early treated PKU 29-51 years. **IQ was significantly correlated to blood phenylalanine** levels in childhood and adolescence, cognition did not seem to deteriorate over a 10 year follow up period, but neuropsychological assessment in adults with PKU showed **neurocognitive impairment** particularly in older adult patients.
Vieira 2017	***Quality fo life and adherence to treatment in early treated Brazilian phenylketonuria pediatric patients*** Peds QL scores lower in PKU treated children. The **harmful consequences for intellectual capacity** caused by **poor adherence** to dietary treatment could explain the observed decrease in all HRQoL scales, particularly in school functioning.
Didycz 2017	***Blood phenylalanine instability strongly correlates with anxiety in phenylketonuria*** 25 PKU non-compliant adolescent study demonstrated **significant correlations with anxiety** and variability of blood phenylalanine concentrations.
Jurecki 2017	***Adherence to clinical recommendations among patients with phenylketonuria in United States*** Adherence to recommend phenylalanine concentrations remains **suboptimal** especially in older patients. There is a need to reduce the number of patients lost to follow up
Bosch 2015	***Assessment of the impact of phenylketonuria and its treatment on quality of life patients and parents from seven European countries*** This study collected a large amount of data from 559 subjects (92 children, 110 adolecents,104 adults) and 253 parents. Good HRQoL was shown, but **negative impacts of PKU** on a patients life included the **emotional** impact of PKU and its management

Sharman 2013	***Qualitative analysis of factors affecting adherence to the phenylketonuria diet in adolescents*** Importance **of strict dietary adherence** in preventing intellectual impairment is recognised, but apathy and nonadherence from diet are more common in adolescence and **normal development is jeopardised**
Thimm 2013	***Health related quality of life in children and adolescents with phenylketonuria: unimpaired HRQoL in patients but feared school failure in parents*** **Adherence** to optimal blood phenylalanine **deteriorated** with age Positive correlation between **poor metabolic control and behaviour** identified by patients
MacDonald 2012	***Adherence issues in inherited metabolic disorders treated by low natural protein diets*** Commonly described dietary **adherence deteriorates** from **10 years**, multifactorial reasons: transfer of responsibility, complexity of diet, neuropsychological impairment
Di Ciommo 2012	***Living with phenylketonuria from the point of view of children, adolescents and young adults: a qualitative study*** Recognised the associated challenges for personal and social life. **Adherence** to a strict regimen, fear of **stigmatisation** and **social isolation** during which food is shared
Ahring 2011	***Blood phenylalanine control in phenylketonuria: a survey across 10 European centres*** Blood phenylalanine control deteriorated with age.
MacDonald 2010	***The reality of dietary compliance in the management of phenylketonuria*** Recognises phenylalanine concentrations greater than optimal treatment target ranges in teenagers and adults showing inadequate compliance. It is established **significant noncompliance** occurs in the treatment of PKU in this age group.
Van Spronsen 2010	***Phenylketonuria: a 21st century perspective*** **Neuropsychological deficits continue** despite treatment Quality of life, nutritional status and psychosocial outcome could be improved

Enns 2010	***Suboptimal outcomes in patients with PKU treated early with diet alone: revisiting the evidence*** **Reviewed the PKU literature** since 2000, important issues need to be revisited growing body of evidence that suggests neurocognitive, psychosocial, quality of life, growth, nutrition, bone pathology and maternal PKU **outcomes are suboptimal**
Bik-Multanowski 2008	***Discontinuation of diet therapy in adults with PKU can lead to neuropsychological abnormalities and emotional problems***. 53 adults previously off dietary treatment, returned to diet and QoL assessments made. Of 53 subjects only 29 managed a return to diet for at least 3 months, and only 10 finished the study period. **Problems** with dietary treatment at **work, cost of prescription foods, poor knowledge** regarding dietary treatment, **severe emotional distress** were cited
Bilginsoy 2005	***Living with phenylketonuria: perspectives of patients and their families*** Caregivers recognised the **negative consequences** of **non compliance** to dietary treatment: difficulties included constraints on **social life**, **food preparation**, **record keeping**
Weglage 1992	***Psychological and social findings in adolescents with phenylketonuria*** Retrospective study 34 early treated PKU adolescents and parents, several psychometric tests. Results: **less autonomy, negative evaluation of school performance, less motivation, low frustration tolerance, negative self-description, less extraversion and impulsiveness**, a feeling not being healthy and a higher dependency on family
Walter 2004	***Blood phenylalanine control in adolescents with phenylketonuria*** From the age of 10 years there is a noticeable deterioration in blood phenylalanine and dietary adherence

Table 2. Impact of dietary non-compliance on neuropsychology

Author/ year	Summary of main findings
Canton 2019	***Neuropsychological profile of children wit early and continuously treated phenylketonuria: systematic review and future approaches*** Systematic review on cognitive outcome in children with early and continuously treated PKU. Findings **specific and central executive impairment** in children was suggested, but the precise cause unknown
Burlina 2019	***The neurological and psychological phenotype of adult patients with early-treated phenylketonuria: A systematic review*** Systematic review over 18y, **common signs tremor and hyperlexia**. **Overall quality of life was good** and comparable to control populations, **no incidence of psychiatric disease** or social difficulties. **Neuroimaging showed brain abnormalities** are present in adults, clinical significance remains unclear
Pilotto 2019	***Cerebrospinal fluid biogenic amines depletion and brain atrophy in adult patients with phenylketonuria*** Review of 10 early treated adult PKU patients and 15 age matched controls, plasma and cerebal spinal fluid was measured. **Significant negative correlations** were found between brain neurotransmitters and phenylalanine levels. **Deficient biogenic amines lead to specific brain atrophy in PKU** patients. A more rigorous phenylalanine control in adult PKU is necessary to prevent neurotransmitter depletion and accelerated brain damage due to aging.

Gonzalez Garcia 2018	***Neuropsychological assessment among children and adolescents with phenylketonuria and hyperphenylalainemia and its relationship with plasma phenylalanine levels*** 26 subjects, diagnosed by new born screening, a trend was observed with a reverse relationship between IQ and concurrent phenylalanine concentrations,median phenylalanine and phenylalanine: tyrosine ratios. Negative relationship between executive functions and concurrent phenylalanine values
Didycz 2017	***Dynamics of hyperphenylalaninemia and intellectual outcome in teenagers with phenylketonuria*** Nonadherence to treatment is a common factor in older PKU patients. This study reviewed the impact of blood phenylalanine fluctuations on cognition in 32 PKU subjects. Over time metabolic control deteriorated, there was a **strong association between IQ verbal scores and blood phenylalanine** concentrations
Waisbren 2017	***Improved measurement of brain phenylalanine and tyrosine related to neuropsychological functioning in phenylketonuria*** 9 PKU subjects, early treated had MRI and neuropsychological tests, brain shows higher brain phenylalanine and lower tyrosine related to poor function, these are useful biomarkers to identify brain dysfunction
Jahja 2017	***Cognitive profile and mental health in adult phenylketonuria: A PKU-COBESO study*** 57 early treated adult PKU subjects with age matched controls had IQ subtests and executive function tests and adult self-report on mental health problems. **Adult subjects had lower IQ and poorer executive functions than controls**, greater internalizing problems. Those **not treated with Kuvan** had poorer outcome on some tests- **suggesting the benefit of Kuvan**

Manti 2016	***Psychiatric disorders in adolescent and young adult patients with phenylketonuria*** Early treated PKU subjects show a higher-than-normal **vulnerability to psychiatric disorders.**
Leuzzi 2014	***Age related psychophysiological vulnerability to phenylalanine in phenylketonuria*** There is a **vulnerability of a decrease in neurocognitive functions related to phenylalanine control**, suggesting a strict control in adolescents is necessary. Neurocognitive and psychiatric problems in adulthood remains a challenge
Castro 2012	***Relationships between phenylalanine levels, intelligence and socioeconomic status of patients with phenylketonuria*** This study assessed intelligence and its relationship with blood phenylalanine concentrations and socioeconomic status in PKU after 6 and 12 years of treatment. Findings: **control of phenylalanine levels and higher socioeconomic status** were **associated with higher IQ**
Gentile 2010	***Psychosocial aspects of PKU: hidden disabiltes a review*** Review article which concludes PKU is a disorder in which **a less than optimal psychosocial** outcome arises from the cumulative impact of relatively mild symptoms, studies show executive function deficits in children and adults with early treated PKU contributing to **hidden disabilities**. These hidden disabilities affect job performance, social relationships and poor executive function planning and organization together with reduced processing speed.

Waisbren 2007	***Phenylalanine blood levels and clinical outcomes in phenylketonuria: a systematic literature review and meta-analysis*** Reviewing 40 studies in early treated PKU children 0-12 years, each **100umol/L increase in phenylalanine shows a 1.3 to 3.1 point reduction in IQ.** There is a significant correlation between IQ and mean lifetime phenylalanine concentrations.
Koch 2002	***Phenylketonuria in adulthood: a collaborative study*** USA collaborative study following 211 infants with PKU, at 30-35 y 73 were followed up. Subjects **maintaining diet had fewer problems** compared to those who had discontinued diet- issues reported off dietary treatment eczema, asthma, mental disorders, headache, hyperactivity and hypoactivity. Lower intellectual and achievement scores. Higher phenylalanine blood concentrations in childhood and adulthood associated with more problems. Abnormal MRI results were associated with higher brain phenylalanine concentrations
Hüijbregts 2002	***Sustained attention and inhibition of cognitive interference in treated phenylketonuria: associations with concurrent and lifetime phenylalanine concentrations*** Study using early and continuously treated PKU with age matched controls. Blood phenylalanine > 360umol/L showed lower speed of information processing, a lower ability to inhibit task induced cognitive interference, less consistent performance and a stronger decrease of performance over time. **Those with phenylalanine concentrations < 360 performed better**. **A strong relationship was found between phenylalanine control and task performance**

McDonnell 1998	***A neurological evaluation of adult phenylketonuria in Northern Ireland*** Specific study on neurological status in 27 PKU adults. All non compliant with diet. **Abnormal neurological features** found in 21/27 cases with significant visual evoked response delay. Periventricular white matter abnormalities were observed in 5/12 who had MRI scans, mean phenylalanine concentration 1224umol/L. **Early treated children have significant neurological morbidity in adulthood**
Thompson 1990	***Brain MRI changes in phenylketonuria. Associations with dietary status*** There is evidence that subtle neurological impairment remains common in early treated subjects. This paper reports on a number of overt neurological impairment with white matter abnormalities on MRI. 34 subjects aged 8-33 y, 25 early treated, 9 late treated. Of the total 34 subjects 32 showed abnormalities on MRI. In the **early treated group, the severity of the MRI changes were significantly and independently associated with phenylalanine concentrations.** Animal studies show hyperphenylalaninaemia increases myelin turnover in a dose dependent way. The effect of phenylalanine on myelin is a lifelong problem to the CNS

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Sapropterin for treating phenylketonuria [ID1475]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 18 March 2021 **email:** NICE DOCS

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Royal College of Physicians (RCP)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	XXXXXXXXXX

Comment number	Comments Insert each comment in a new row.

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Sapropterin for treating phenylketonuria [ID1475]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 18 March 2021 **email:** NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	At the RCP we have had three separate responses to this appraisal consultation document. These are from the British inherited Metabolic Disease Society (BIMDG) and from two RCP Fellows: an RCP recognised expert Dr Robin Lachmann who treats a significant number of these patients and from Dr Emma Vardy who cares for patients with neurodegenerative disease in older age and is a parent of a child with phenylketonuria (PKU). The RCP endorses the view of the BIMDG but in addition would like to add the following points: We have serious concerns about stopping sapropterin treatment at the age of 18 and recommend that this is changed. The decision to recommend stopping sapropterin treatment at the age of 18 seems arbitrary and will coincide with a particularly vulnerable period in these young people's lives. We are very concerned that stopping Kuvan at the age of 18 will result in significant numbers of young adults with PKU discontinuing diet. This transition period is already known to represents the highest risk time for reduced compliance and becoming lost to treatment, for people with PKU. There is some evidence that raised phenylalanine (Phe) may have a wider impact than just on brain development with higher rates of depression and a wide range of other medical conditions. We understand the need for cost effectiveness but note there is some evidence that suboptimal dietary adherence is associated with poorer quality of life scores. To ensure optimum outcomes by treating young people until neurodevelopment is completing, then we recommend treating until at least the age of 25.
2	We have serious concerns that Sapropterin is not being offered as a first line treatment to women with PKU. There is a great deal of evidence concerning the teratogenic effects of Phe and the need for women with PKU to obtain strict metabolic control throughout pregnancy. There should be no question of the cost-effectiveness of sapropterin in this setting. Women with PKU who are planning pregnancy, and the healthcare professionals looking after them need access to every means possible of maintaining phenylalanine levels within the target range for pregnancy. On Page 7 of the consultation the committee concluded that high blood Phe levels in pregnancy can have harmful effects on the unborn child. Early control of Phe levels, ideally before conception, would reduce the risks. Data indicate clearly that use of Sapropterin in pregnancy is safe and prevents the maternal PKU syndrome. Consideration should also be given in the vulnerable period post-partum while mothers are adjusting to caring for their children and managing a tightly restrictive diet is virtually impossible. We suggest that all women of child-bearing age (14-45 years) are assessed for Sapropterin responsiveness – and those who are responsive to be offered Sapropterin as a first-line option when they are actively planning pregnancy (the pre-conception period) and for the duration of pregnancy and for a short period postpartum.

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Sapropterin for treating phenylketonuria [ID1475]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 18 March 2021 **email:** NICE DOCS

3	NICE has not given any recommendations on how Sapropterin-responsiveness should be determined longer-term. We have concerns about the lack of clear criteria concerning sapropterin responsiveness and the lack of definition of what constitutes a satisfactory response to treatment. One of the major issues in using sapropterin to treat PKU is that it has different effects in different patients. It is important to precisely define which patients are to be considered responsive to sapropterin. This involves describing the method of testing as well as what constitutes an adequate response in terms of lowering Phe and/or increasing natural protein intake. Sapropterin is used as an adjunct to diet. Dietary treatment on its own can be used to achieve target phenylalanine levels in all patients, although this can be very challenging. Therefore, for different patients the goals of adding sapropterin to dietary treatment are different. For some, the goal will be to reduce Phe levels into the normal range whilst for the majority, the goal will be to allow patients to maintain target phenylalanine levels with less dietary restriction. Because of this it is also very important to define criteria for what constitutes a satisfactory long-term response to sapropterin. Without clearly defined definitions of responsiveness and response, it will be very difficult to translate any NICE recommendations into clinical practice. The final recommendations need to address these issues in detail. This has previously been done by a policy working group convened by NHSE and the committee might find it very useful to look at the NHSE policy proposal the 'Interim Clinical Commissioning Policy: Sapropterin for phenylketonuria (All ages)'. Although many patients in the UK are not currently genotyped, data regarding the determination of Sapropterin-responsiveness by *PAH* genotype is also increasing (see http://www.biopku.org/home/biopku.asp).
4	We would request that the review date of the policy is reduced from 3 to 2 years to enable new evidence to be considered as further research becomes available. We are aware that several studies are near publication.

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more

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information.

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- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[redacted] National Society for Phenylketonuria [redacted] [Metabolic Specialist Dietitian] [redacted]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
Name of commentator person completing form:	[redacted]

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Sapropterin for treating phenylketonuria [ID1475]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The recommendation that sapropterin should be used until the age of 18 and then stopped is inappropriate and dangerous. The reasons are set out below: **Difficulties Starting diet only treatment at age 18 (and difficulties experienced by all on PKU diet):** The European Guidelines for Diagnosis & Management of PKU state that treatment should be lifelong (van Spronsen et al 2017), so a patient stopping sapropterin at age 18 would need to start dietary treatment. The diet is commonly restricted to about 10g protein per day (Ford et al 2018), and protein containing foods are counted and measured down to 0.3g protein per serving. The complexity of the diet is beyond any other dietary regimen and has evolved over 20-30 years and details have only just been agreed by specialists (Evans et al 2019). It is necessary to plan, shop for ingredients, weigh foods and cook/prepare foods with great care. Baking with low protein products and no egg takes quite some skill and not everyone acquires these skills. The time commitment needed for a low protein diet is considerable and has been measured. A recent NHS Commissioning policy noted that: *"Families and patients have been found to **spend on average 19 hours per week** on dietary compliance, thus affecting every aspect of life and testing patient's self-control (MacDonald A et al 2016)"* The above relates to people who did *not* have impaired intellectual or executive functioning. In individuals with impaired neurocognitive functioning (a recognised result of undertreated PKU, well evidenced by many including Palermo et al 2017)) the time taken to manage the diet is longer. Further evidence shows that, in order to achieve the best health outcomes for adults self-managing their PKU, ***part time working, and flexible working patterns were the only ways to achieve good control*** in a group of adults with PKU (Riva et al 2017). Someone stopping sapropterin and starting diet would be compromising their ability to attend college full time or do a full-time job. The current treatment regimen consists of specialist low protein products to provide energy and variety and a protein substitute providing amino acids without the phenylalanine – these are only available on prescription. In a peer review paper (Ford et al 2019) reporting access issues to products via the NHS 59% of responses (over 250 respondents) showed difficulty accessing

	basic low protein foods (bread, pasta) and 33% protein substitute. 36% of responses said problems had occurred for over a year. **18% reported that the local NHS authority had refused, restricted or had a policy to block treatment access; 27% cited GPs declining requests or restricting prescription amounts.** This all equates to treatment disruption for patients with PKU in England, and poorer outcomes for all. Patients experience food insecurity and treatment insecurity on an ongoing basis. Aspartame – is a phenylalanine ester and thus must be avoided in PKU. The additional scrutiny of checking all food ingredient labels for aspartame in food, drinks and drugs intensifies the complexity of management, so this is a further difficulty for PKU patients of all ages. In peer reviewed evidence, Newbould and team (2021) reported that 74% of 200 PKU patients surveyed had accidentally ingested aspartame. **23% respondents had been prescribed medicines containing aspartame and 75% said that medicines were not checked by medics when prescribed**. Further evidence about how difficult the diet can be, is published evidence following analysis of over 460 standard food items, reported that **55% of food labels were unclear** (Kravela et al 2020) . Finally: data less than a year-old shows that the majority of English adults (with or without PKU) are overweight or obese; 67% of men and 60% of women. **If the general population cannot manage their own energy intake to match energy expenditure (a well understood concept), how can people with PKU restrict their diet** to an average of 10g protein daily, which seems to be undermined by a number of systemic failings in the NHS and public health strategy? There is clear evidence *globally and in the UK* about worsening metabolic control as PKU patients become adolescents and adults (Walter et al 2002, Mundy et al 2002, Walter & White 2004 and Ahring et al 2011 all include UK based adult patients). NICE does not provide any evidence that the future would be different and that 18-year-olds stopping sapropterin would have safe metabolic control and good outcomes in this treatment pathway. An example in my clinical experience is women with mild PKU are taught to restart diet – they may have no experience of implementing a PKU diet and needs to learn the diet – this can take multiple (50+) hours of intense work and dedication on the part of all – these women are not true proxies for this sapropterin to diet scenario, as the pregnancy diet is a temporary intervention only. Patients returning to diet, in my clinical experience, generally do not succeed on an ongoing basis. There is no evidence to suggest that this unethical proposal NICE has for offering sapropterin to responsive patients until the age of 18 would enable them to continue safely into adulthood with good metabolic control, and good outcomes. All evidence suggests the opposite.

Sapropterin for treating phenylketonuria [ID1475]

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	van Spronsen F et al (2017) Key European guidelines for the diagnosis and management of patients with phenylketonuria. The Lancet Diabetes and Endocrinology Vo 5, Issue 9, September 2017, Pages 743-756 Ford S, O'Driscoll M, MacDonald A. Living with Phenylketonuria: Lessons from the PKU community. Mol Genet Metab Reports. 2018;17(August):57-63. doi:10.1016/j.ymgmr.2018.10.002 Evans S, Development of national consensus statements on food labelling interpretation and protein allocation in a low phenylalanine diet for PKU; Orphanet Journal of Rare Diseases (2019) 14:2 MacDonald A, Smith T, de Silva S et al; The personal burden for caregivers of children with phenylketonuria: A cross-sectional study investigating time burden and costs in the UK; Molecular Genetics and Metabolism Reports 9 (2016) 1–5 Palermo L et al, Cognitive outcomes in early-treated adults with phenylketonuria (PKU): A comprehensive picture across domains. Neuropsychology. 2017;31(3):255-267. Riva MA1, Madotto F, Turato M, Salvatici E, Indovina S, Giovannini M, Riva E, Cesana G. (2017) Work activity and phenylalanine levels in a population of young adults with classic PKU. Med Lav. 2017 Apr 21;108(2):118-122 Ford S, O'Driscoll M, MacDonald A; Prescribing issues experienced by people living with phenylketonuria in the UK; Mol Genet Metab Rep. 2019; 21 100527 Newbould, E.; Pinto, A.; Evans, S.; Ford, S.; O'Driscoll, M.; Ashmore, C.; Daly, A.; MacDonald, A. Accidental Consumption of Aspartame in Phenylketonuria: Patient Experiences. Nutrients 2021, 13, 707. https://doi.org/10.3390/ nu13020707 Kraleva, D.; Evans, S.; Pinto, A.; Daly, A.; Ashmore, C.; Pointon-Bell, K.; Rocha, J.C.; MacDonald, A. Protein Labelling Accuracy for UK Patients with PKU Following a Low Protein Diet. *Nutrients* 2020, *12*, 3440. https://doi.org/10.3390/nu12113440 Walter J et al. (2002). How practical are recommendations for dietary control in phenylketonuria? The Lancet. 2002;360(9326):55-7. Mundy, Helen; Lilburn, Maggie; Cousins, Alison; Lee, Philip.Dietary control of phenylketonuria; The Lancet; London Vol. 360, Iss. 9350, (Dec 21, 2002): 2076. DOI:10.1016/S0140-6736(02)11959-3 Walter JH and White, FJ; Blood phenylalanine control in adolescents with phenyl-ketonuria; Int J Adolesc Med Health 2004;16(l):41-45. Ahring K et al. (2011). Blood phenylalanine control in phenylketonuria: a survey of 10 European centres. European Journal of Clinical Nutrition. 65(2):275.
2	*The statements on the risks of long-term brain damage in adults are inconsistent and lack robust evidence or investigation. "Clinical experts explained…..In adults, high Phe concentrations can result in short-term symptoms, which are considered reversible by lowering Phe levels through diet."* The literature suggests that white matter changes caused by high phe in the brains of adults with PKU is more reversible than brain damage incurred in children. However,

	there is no conclusive evidence that brain damage in adults is fully reversible. For example, Cleary in published on this 26 years ago, and 2 months ago, further imaging evidence is provided by Clocksin et al, 2021 in MGM) have found improvements following phe level reduction in adults. Even after improvement, white matter integrity in the PKU patients in these studies **continued to be compromised** relative to healthy non-PKU individuals. In practice, there is no evidence of successful cohorts of patients (except preconceptually and in pregnancy) returning to diet and regaining control of their PKU – there is evidence of patients who were unable to (Bik-Multanowski 2008), so the reversibility of white matter damage in adults with PKU is entirely theoretical and not evidence based. Adult patients who stop the PKU diet experience poor executive functioning, information processing (worse reaction times, sustained attention, poor working memory) and mood (increased inhibition, anxiety, depression and low self-esteem) compared with adults who have continued phenylalanine restriction throughout life and also metabolically healthy controls. However, even adults with continuously treated Pku on diet, do see experience decline in their executive functions. Other study data distinguishes specific poor executive function linked to *concurrent* metabolic control – ie that in adulthood - Romani et al 2017 and 2019 – such as sustained attention. If adults have poor sustained attention, how can they reverse their white matter changes by successful dietary implementation in a regimen that is complex and when prescribing practices, labelling legislation and public health practices do not support this. Finally: case control study data evidences adults with PKU have compromised social cognition – this in itself may see inconsequential – combined with the need for ongoing self-advocacy for optimal outcomes for an intrusive treatment for a rare disease, then it contributes to difficulties with the diet – people cannot assert their needs in various life situations and thus fall out of control (negotiating GP, pharmacies, work situations etc). Refs: Cleary MA et al. (1995). Magnetic resonance imaging in phenylketonuria: reversal of cerebral white matter change. The Journal of Pediatrics. 127(2):251-5. Clocksin, HE et al Inter- and intra-tract analysis of white matter abnormalities in individuals with early-treated phenylketonuria (PKU), Molecular Genetics and Metabolism, 132; 1, 2021, p11-18, ISSN 1096-7192; https://doi.org/10.1016/j.ymgme.2020.12.001 M. Bik-Multanowski, B. Didycz, R. Mozrzymas, M. Nowacka, L. Kaluzny, W. Cichy, B. Schneiberg, J. Amilkiewicz, A. Bilar, M. Gizewska, A. Lange, E. Starostecka, A. Chrobot, B.I. Wojcicka-Bartlomiejczyk, A. Milanowski. Quality of life in noncompliant adults with phenylketonuria after resumption of the diet. J Inherit Metab Dis. 2008 Dec;31 Suppl 2: S415-8. Jahja Rianne (2017) et al; Long-Term Follow-Up of Cognition and Mental Health in Adult Phenylketonuria: A PKU-COBESO Study; Behav Genet; DOI 10.1007/s10519-017-9863-1

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	Palermo L et al, Cognitive outcomes in early-treated adults with phenylketonuria (PKU): A comprehensive picture across domains. Neuropsychology. 2017;31(3):255-267. Romani C, et al (2017) The impact of phenylalanine levels on cognitive outcomes in adults with phenylketonuria: Effects across tasks and developmental stages. Neuropsychology. 2017 Mar;31(3):242-254. Cristina Romani et al; Adult cognitive outcomes in phenylketonuria: explaining causes of variability beyond average Phe levels; Orphanet Journal of Rare Diseases (2019) 14:273 Jahja R, et al; Social-cognitive functioning and social skills in patients with early treated phenylketonuria: a PKU-COBESO study; J Inherit Metab Dis (2016) 39:355–362
3	*Clinical experts noted that just over 50% of adults with PKU are on a protein-restricted diet, while about 30% of adults have stopped their diet and the other 20% have difficulties maintaining it.* I am unaware of any evidence, nor was it provided, which supports these figures; there is evidence to the contrary. Incidence and prevalence of PKU in England, compared to the 2,000 people NICE mentions currently in PKU care and the clinical expert's comments are all inconsistent. Expected number of patients: NICE notes that 2,000 patients are receiving PKU care in the NHS currently. Yet >2,400 have been diagnosed by the Public Health England Newborn screening programme since 1969. Basic diagnostic tests were used from 1951-1969 - 1,000 babies would have been born then and diagnosed then or subsequently via sibling screening or investigations. How can clinical experts know if 50% of these adults with PKU are on diet if they are not in PKU care? People who are not in follow up will not be on diet. 1. Many adults with PKU are no longer followed up by specialists. 2. Patients were discharged in the past by medics who believed their brains had finished developing and PKU treatment cessation was safe and appropriate from the age of 4 through to the age of 18-19 (active discharges were happening from all metabolic care as recently as 10 years ago). 3. Patients are lost to follow up still and on an ongoing basis due to poor transition arrangements (I have contacts with these patients on NSPKU helpline). 4. The treatment status of any of the above groups of adults in the UK cannot possibly be known as no arrangements are in place to find them. 5. The percentages mentioned do not even apply to adult patients in clinics as there are insufficient blood phenylalanine results or published data to support this.

Sapropterin for treating phenylketonuria [ID1475]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 18 March 2021 **email:** NICE DOCS

	There is a responsibility of health care providers in the UK to make provision for treatment for all adults with PKU and optimise the outcomes. NICE and/or its clinical expert has overestimated the use of diet amongst adults with PKU in the UK and thus ignored potential adverse outcomes of those not on diet. Finally: in my clinical experience the 50% of adults on diet and "not struggling" does not relate to adults with PKU, even those receiving metabolic follow up. In published survey data (Ford et al 2018) 73% of adults (n=209/286) said they found dietary management difficult. Eg female patients in Bristol – are rarely able to take the prescribed dose of protein substitute, rarely send bloodspots. An example: patient P never misses any appointments; she tries very hard to have a low protein diet but she takes 5 out of 21 doses of her amino acids each week Taking protein substitute is fundamental to the PKU diet regimen. She is not alone in this and both direct experience of patients in my NHS work, work with those seeking help from NSPKU, and published evidence backs this up. Thus I refute the clinical expert comments, from a "whole UK PKU cohort" perspective and within clinical experience perspective. Ford S, O'Driscoll M, MacDonald A. Living with Phenylketonuria: Lessons from the PKU community. Mol Genet Metab Reports. 2018;17(August):57-63. doi:10.1016/j.ymgmr.2018.10.002
4	*Consideration of Maternal PKU Syndrome:* NICE acknowledges that maternal phenylketonuria (PKU) syndrome is caused by high blood phenylalanine (Phe) levels during pregnancy having a teratogenic effect on the developing foetus which can result in intrauterine growth retardation, facial dysmorphism, developmental delay, intellectual disabilities, microcephaly and congenital heart disease (CHD). In my role I have managed or supported patients with PKU either through pregnancy or through preconception and then pregnancy and had contacts with women via NSPKU work (>40 women; none have ever accessed sapropterin). Most women have reported poor control during their pregnancy – frequently in the first trimester. The first trimester is fraught with difficult to manage sickness, needing to eat as low as 3g protein daily; changing medications to suit the symptoms, and bloodspot testing three times a week (latter ongoing for full pregnancy). The current policy to access sapropterin is ineffective and dangerous – in particular it means sapropterin unlikely to be successfully given to patients quickly enough/early enough in pregnancy to help avoid poor outcomes in offspring.

Sapropterin for treating phenylketonuria [ID1475]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 18 March 2021 **email:** NICE DOCS

	Strict metabolic control before and throughout pregnancy reduces foetal risk if dietary control is achieved **before** conception and maintained throughout pregnancy. The European Guidelines state that treatment should commence pre-conception for maternal PKU, and it emphasises that significant effort should be undertaken to avoid any unplanned pregnancies. The data that is available suggests that current management of females with PKU results in misery for many young women, girls and older women. In the peer reviewed publication from the NSPKU survey 73% of women (n= 300) expressed concerns, fears and distress about pregnancy. 60% were concerned about harm they may cause to a baby, 54% had anxiety about their ability to maintain blood Phe within target, and 48% feared unplanned pregnancy. Some were concerned that it may be unsafe to have a baby as a woman with PKU (39%, n=107); some worried about their parenting skills (16%, n=43), and women even described how they avoided sexual relations. 8% of women were too embarrassed to discuss pregnancy in clinic; 9% said they had a pregnancy termination due to PKU, 14% had a miscarriage and 8% had more than one miscarriage. In the post-natal period, of 93 women, 48% had low mood or sadness, 41% were depressed, 25% felt unable to cope, 33% said they could not care for their PKU as well as their baby, 14% (struggled with childcare needs and 4% worried they might hurt themselves or their baby. 14% thought that child health or developmental problems were linked to PKU. UK pregnancy outcome data is poor and it is not relevant to attempt to compare it with pregnancy data elsewhere. Published data on UK pregnancies include Jovanovic et al 2011 reported on 42 women of reproductive age with PKU and of the 20 pregnancies, only 9 had healthy outcomes. Adams et al (2017) reported on pregnancies in 17 women in Glasgow, 4 out of 17 had offspring with congenital abnormalities. Other data (Maillot et al 2008 and Lee 2005) showed that there is significant negative impacts on offspring IQ and other important markers, relating to blood phe control and whether the mothers were on a preconception diet or started PKU diet after conception. Although this data is 13 years old there is no reason to believe that any improvements in outcome have been realised by the IMD clinical teams caring for women with PKU in the UK. For instance, the rate of planned vs unplanned pregnancies and on diet vs off diet is unlikely to have changed. One London centre for IMD in adults reported on diet status at conception – Cook et al 2018 and 10 of the 22 pregnancies were conceived outside of the desired pregnancy range of phe control; **in another large centre in the UK, between 2010 & 2017 an average of 54% of patients conceived offspring outside of the target range of phe**. Thus the instigation of tight metabolic control for pregnancy (<300muol/l) is starting too late for the optimal outcomes in these unplanned pregnancies and the current sapropterin policy for access *after* poor metabolic control is demonstrated in pregnancy fails to prevent foetal exposure to the highly teratogenic effects of phenylalanine.

	Ford et al 2018 also showed women stopped dietary management shortly after childbirth. They could not cope with the pressures of strict dietary management and caring for their baby (also evidenced in Cook et al 2018). Many described anxiety, depression, tiredness and inability to focus well after the birth of the baby and some described how they struggled with day-to-day childcare. Postpartum depression in the general population is known to adversely affect infant caregiving activities such as breast feeding and sleep routines (Field et al 2010); there remains a high probability that postnatal depression may be exacerbated by higher blood Phe concentrations. It has been shown that women who remain on treatment post pregnancy are likely to have fewer mental health issues and are better able to cope with parenting (Rohr et al 2004) which in turn, has an important impact on the cognitive outcome of their children. Furthermore, women needed guidance about their own nutritional needs during breastfeeding whilst on the PKU diet post birth. All evidence points to ongoing poor reproductive outcomes for women with PKU in the UK and their offspring - needing interventions ranging from cardiac surgery to statements of special educational needs throughout the education of the offspring (and reduced life chances). Of note, some women with milder forms of PKU (who would be more likely to be sapropterin responders) have not ever done the diet themselves yet have to learn this diet regimen very intensively for preconception and pregnancy purposes. Of note – there is a major health campaign around improving outcomes via influencing the first 1,000 days of life, recognising how important they are for the child's health and development in later life. The window of time preconceptually, post conception and pre birth can determine health outcomes for the whole of adult life. Maternal health is vital to the outcomes of children, especially in their early years. Mothers should be supported during pre-conception, the antenatal period, labour and birth, and the post-natal period. The benefits of using sapropterin would be to make tight metabolic control in the preconception period feasible for many more women that dietary control does now; sapropterin given throughout pregnancy would reduce the difficulties seen in achieving control in the first trimester of pregnancy and post delivery, sapropterin would allow for best cognition and mental health of the mother in the crucial first weeks of motherhood. **There should be parity surrounding outcomes in children born to women with PKU and children born with PKU and NICE's sapropterin recommendation is failing on this.** **Case Study A:** [redacted]

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[redacted]

Refs:

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5	*The committee understood that some people may have greater difficulty adhering to conventional dietary management of PKU and are at higher risk of being unable to control their phenylalanine. Some people may also have difficulty accessing healthcare services.* NICE has not mentioned late treated or untreated patients with PKU at any stage; these patients are characterised by learning difficulties, challenging behaviours and also epilepsy. Data shows that patients with learning difficulties have reduced challenging behaviours when they keep their blood phenylalanine controlled and a number of clinical studies advocate phe restricted diet in adults with late diagnosed or previously untreated PKU due to improvements in subjective measures of alertness, mood, irritability, concentration, destructive behaviour, quality of life and adaptive behaviour (Murphy et al 2005; Fitzgerald et al 2000; Koch et al 1999; Baumeister et al 1998; Pavone et al 1993). Patients experience less anxiety and have fewer behavioural interventions, restraints etc when on a PKU diet (Lee et al 2009). This is clearly beneficial to achieve good metabolic control for patients, and the benefits can be felt by patients and carers alike and is cost effective compared to staffing numbers needed to care for people with challenging behaviours. The diet cannot be easily administered to all of these patients in care homes. There late treated patients with PKU in England, are in care homes and some are being cared for by elderly and vulnerable parents or siblings. These patients have more than one protected characteristic under the Equality Act 2010 and should not be forgotten. **Case Study P** Regular Caller P has late treated PKU and has diagnoses of paranoid schizophrenia and mild learning disability. P would like to be on diet but cannot be as she lives by herself. P does not have the inhibitory control to be on diet, however she has chronic ongoing mental health issues, needing mental health input daily or more frequent, or being a psychiatric inpatient. P has called the NSPKU helpline on average 4 times a week for the last 4+ years wanting to try the low phenylalanine diet (as long as I have been in post – so

	this is over 800 calls. Sapropterin would be accessible as a means to treat this patient's high phenylalanine levels, in a way that diet is completely inaccessible for her. The NSPKU regularly has helpline calls from **many patients like this**, who live semi-independently, and many of their activities of daily life are done by either family members or support workers. We know of other patients who live with elderly parents and would not be able to access the diet but could access sapropterin, and many patients in case homes who similarly are difficult to treat with the PKU diet. In many cases these patients have symptoms or behaviours which, evidence suggests, would be improved by lower phe levels. The current NICE draft guidance is discriminatory against the learning disabled patients with PKU as it simply does not consider their needs at all; this likely applies to most patients with PKU who were born before 1969. Refs: Murphy G, Johnson S, Amos A, Weetch E, Hoskin R, Fitzgerald B *et al.* (2008) Adults with untreated phenylketonuria: out of sight, out of mind. *Br J Psychiatry J Ment Sci*; Dec; 193(6); 501-2 Fitzgerald B., Morgan J., Keene N., Rollinson R., Hodgson A., Dalrymple-Smith J.(2000) An Investigation into D Treatment With Previously Untreated Phenylketonuria and Severe Intellectual Disability; J. Intellect. Disabilit 44 (1); 53-59 Koch R., Moseley K., Ning J., Romstad A., Guldberg P., Fleming G., (1999) Long-term Beneficial Effects of the Phenylalanine-Restricted Diet in Late-Diagnosed Individuals With Phenylketonuria; Mol. Genet. Metab; 67; 1 155 Baumeister and Baumeister (1998) Dietary Treatment of Destructive Behaviour Associated with Hyperphenylalaninemia; Clin. Neuropharmacol. 21 (1) 18-27 Pavone L., Meli C., Nigro F., Lisi S., Raimondo Di., Mollica F., (1993) Late Diagnosed Phenylketonuria Patients: Clinical Presentation and Results of Treatment; Dev. Brain Dysfunct. 6; 184-187 Lee P., Amos A., Robertson L., Fitzgerald B., Hoskin R., Lilburn M., Weetch E., Murphy G., (2009) Adults with l diagnosed PKU and severe challenging behaviour: a randomised placebo-controlled trial of a phenylalanine-restricted diet J Neurol Neurosurg Psychiatry; 80:6 631-635
7	There is clearly much more published data that shows PKU in adulthood to be burdensome, symptomatic and difficult to treat with the PKU diet – I will not cite it all here. In my role at NSPKU I answer the helpline so I am aware of various patient experiences and clinical situation. The below patient gave me permission to share this which illustrates the statistics shown in NSPKU surveys about access to prescribed treatment items in the UK:

Sapropterin for treating phenylketonuria [ID1475]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 18 March 2021 **email:** NICE DOCS

	A Case Study about experiences of adults in the UK system and abroad: **Case study C** C has PKU and is healthy from age 0-23, living in 4 different countries (including Scotland, England, France), she arrives in London July 2016. Her GP refuses to make a specialist referral - she makes 10 attempts to get referred - there is a 4-month delay. C changes GPs but there are delays to a specialist referral by another 2 months. C sees a specialist who supports her continuation on the PKU diet, but her GP pharmacist says the practice is "Unable to Prescribe" PKU treatment. C finds a new GP Surgery (No 3), and the GP says her PKU script would "destroy surgery budget". Diagnosed with acute depression and anxiety – commonly associated w PKU, C becomes an **Emergency Acute Psychiatric Inpatient. Her inpatient stay is 25 days long.** Even as a psychiatric inpatient, C's GP declined to provide PKU treatment until her psychiatrist intervened. C registers with her 4th GP and a new pharmacy. C requests her script monthly; last month surgery blocked script until her blood pressure check is performed (she is 25 years old and works full time). She runs out of food and treatment again because she cannot take time off for the blood pressure check. Total cost of diet in 1 year: £12,000. Cost of Above Interventions unknown. Above patient contacted NSPKU helpline in 2017. In 2019 she moved overseas, and having been a sapropterin trial patient as a child she was granted sapropterin from May 2019: - Protein tolerance increased from 20g/day to 60g/day (for levels under 400umol/L); or 80g a day to keep my levels under 600g/umol. - Now eats a completely normal vegetarian diet and rarely require low-protein foods. - Has really increased energy levels - I took up competitive rowing and began competing in regattas, and also began long-distance cycling and strength training. - No longer hungry all the time! - Weighed 72kg when started Kuvan (overweight BMI); the effect of increased protein in the diet meant that without 'trying', weight dropped to 64kg (healthy BMI). - Stable mood and mental health, consistent high performance in high-stress roles at work. - Easier to travel and able to be deployed last year to assist with coronavirus response overseas (works for the government).

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.

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NICE National Institute for Health and Care Excellence

Sapropterin for treating phenylketonuria [ID1475]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 18 March 2021 **email:** NICE DOCS

- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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NSPKU questionnaire responses – adults
ID1475 sapropterin for treating phenylketonuria

Questions

Q1. **Section 1 Recommendations: Do you agree with NICE's recommendation which says that: Sapropterin (ie Kuvan) is recommended as an option for treating people with PKU only if they are under 18?**

Q2. **Section 1 Recommendations : Do you have comments on the proposal to let children take Kuvan (sapropterin) until the age of 18 and then stop? (Your experiences about being a teenager with PKU and learning to manage dietary treatment on your own are relevant.)**

Q3. **Section 3 - Long term brain damage in adults - NICE has said: "...adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25." NICE has also said "and there is no risk of long-term brain damage in adults". What is your opinion on NICE's statements about brain damage in adults?**

Q4. **Section 3 - Long term brain damage - Do you have experience from your own knowledge or experience about long term brain damage in adults? Is there any evidence you want NICE to take into consideration (including from your own personal or family experience?)**

Q5. **Section 3 - Symptoms and quality of life. - NICE has said "Many adults describe the effects of high Phe levels as 'brain fog', forgetfulness, tiredness, confusion, low mood and feelings of irritability. This can affect their ability to control their diet and maintain adequate blood Phe levels." Do you have additional comments? What effect does high phe levels have on your quality of life?**

Q6. **Section 3 - Long term effects of high or low phe levels on quality of life in adults : NICE say it is not necessary to take into account the long term effects of high or low phe levels in adults (ERG Report paragraph 5.3) when calculating cost effectiveness for adults. Do you agree? Do you think that having high phe levels in the past can affect your future health or life experiences? If you have information or experience to share, write it here.**

Q7. **Section 3 - Physical and mental effects of PKU and the healthcare costs associated with them. - NICE did not include healthcare costs associated with looking after patients with PKU symptoms or health problems associated with PKU. Do you think there are significant healthcare costs associated with PKU (for example treatment for depression, or gut problems?) Do you want to explain the health issues you have which are related to PKU or living with the PKU diet?**

Q8. **(Carer disutility) - NICE did not take into account the effect that PKU has on family members that help manage PKU symptoms or PKU treatments. What is your opinion? Do you think NICE should taken into account the impact of PKU on other family members? Do you have experience to share?**

Q9. **Equalities - treatment of different groups. NICE said some people may have greater difficulty managing PKU through diet. NICE have said the groups of people who may be disadvantaged include - "People who face such difficulties include: people with a learning disability, sensory impairment, or cognitive impairment• autistic people and people with comorbidities such as diabetes and gut disorders• people on low incomes, living in poor or in insecure housing• certain ethnic groups including people who do not speak English and Gypsy, Roma and Traveller communities• people in social care settings• women with PKU who need to establish controlled phenylalanine levels before conception to avoid damage to the unborn baby." NICE concludes that it was not possible to recommend KUVAN in any group of adults "due to the cost effectiveness estimates in adults". Do you have comments about some people who have extra problems managing PKU because of their situation? Do you think NICE has properly considered treating people fairly?**

Q10. **Women with PKU and their children - NICE has said : "The committee was not aware of any evidence to estimate the benefit to the unborn child of enhanced Phe level control or greater natural protein consumption from conception to birth and accepted that this is challenging to model." NICE has not recommended Kuvan (sapropterin) to help women manage the risk of Maternal PKU. What recommendation do you think NICE should make?**

Q11. **Women with PKU and their children - NICE has said they welcome comments and further evidence on the potential use of Kuvan (sapropterin) in women with PKU of childbearing age, or those planning pregnancy, to prevent harm to the unborn child. Do you have comments or evidence to give to NICE? Things you can think about writing are....- worries about pregnancy and contraception and how this makes you feel, experiences of controlling phe levels in pregnancy, experiences after pregnancy when you have a new baby or a family, your knowledge of effects on babies/children of phenylalanine levels.**

Q12. **Women with PKU and their children : NICE has not included the costs of preventing neurological damage to the children of women with uncontrolled PKU (ERG report, section 5.5) in their costs calculations. Do you have any comment?**

Q13. **Do you have any additional comments on the draft recommendation or the evidence NICE has considered?**

Responses

Respondent 1

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Giving kuvan to children and stopping at 18 is just horrible the Pku diet for me is so much harder as an adult then when I was a child/teen where my mum did a lot of the day to day running of my Pku as an adult you have to balance work life family everything and then stick to your Pku is not easy cooking two or three different meals. And taking it off someone who had been able to eat a fair bit on it to then have to drop the amount they can have is very unfair and will be extremely hard.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. I know many adults who came off diet and have trouble with day to day task due to this such as memory loss and struggling to concentrate meaning they aren't able to hold down a job for long effecting their whole lives.

Q5. High phe levels give you constant headaches and tiredness to the point where you don't want to move you have no motivation and so it doesn't just effect you but those around you to, and getting back on track takes a lot it's a never ending circle the higher your level gets the harder it is to get it back under control.

Q6. *[no response given to this question]*

Q7. *[no response given to this question]*

Q8. *[no response given to this question]*

Q9. *[no response given to this question]*

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. Being a woman who has had two children, going though this is extremely hard and emotional getting sickness due to being pregnant and knowing you have to eat and you have to take supplements and only being allowed to have 1g of protein a day (a bag of 25g crisps are 2g) it one of the hardest things I have ever done and knowing that I would Likely be a responder to kuvan but that it isn't available to adult is heartbreaking when you think of the people who get things like help to lose weight or help to stop smoking these people are this way though their own actions, us Pku adults did not choose to be born with Pku we can't help the fact that managing this diet is so hard and trying to live a full normal life at the same time. This drug would help so many people and yes not all but the ones it will help it will change their life and make their lives easier and healthier and happier.

Respondent 2

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I think this is cruel to children, being brought up with an almost normal diet and not knowing any different, and then at 18 having this stripped of you. I think it is cruel when, at 18, you are facing a big change in your life, by becoming an adult. You have a lot of emotions and difficulties of a teenager but you begin to have adult responsibility, so life is tough as it is. To add on trying to manage a strict PKU diet for the first time ever, just seems impossible and like you are being set up to fail.
Also, I think it is ridiculously unfair on adults. I think it is a form of age discrimination, to not care for and treat adults with PKU even though they do have very serious long term health issues, without the Kuvan and trying to stick to an impossible PKU diet.
I would also like to have the option of having children in a few years, but the thought of having a disabled baby because the PKU diet has been so incredibly hard to follow (on top of how hard pregnancy is in the first place) really frightens and upsets me. I feel it is my human right to be able to have a healthy baby, and Kuvan can make that happen for me and this recommendation is denying me of this human right.

Q3. I do not agree with NICE's view

Q4. This is in fact wrong. I now have a diagnoses of dyslexia and was diagnosed at age 23 whilst studying my second degree. I have been informed by my doctors this is a result of not being able to stick to my PKU diet.
I think it's ridiculous to think that for many many years of being an adult. A poor PKU diet is definitely going to have serious and long term effects. As for me I find I experience brain fog, concentration issues, memory issues, slow processing issues, from any form on non compliance with my diet and this appears constant and my battle to stick to my PKU diet is ongoing. I find it impossible to stick to and it upsets me so so much.

Q5. Being aware of the consequences of not sticking to PKU diet does NOT help you control it. We are only allowed 15% of food. You cannot understand the effects it has on you mentally to try and stick to that on a long term basis without it effecting your mental health.

Q6. Yes I agree. I have experienced first hand how having high Phe levels, significantly deteriorates my quality of life.

Q7. Health issues I have had relating to PKU are - poly cystic ovaries, obesity, depression, anxiety, skin rashes, squint in my eye (Poor PKU diet worsens it. Requires an eye operation every 5 years), and dyslexia. These are the health problems I have that cost the NHS lots of money on a yearly basis as a result of a poor PKU diet.

Q8. I think my behaviour, overall mood can be a serious challenge to my partner and family, they often feel helpless as they know how much it effects me but can't do anything to help.

Q9. I think it is completely unfair to not give Kuvan to women trying to conceive. It puts the mother and baby at a significant risk during pregnancy and birth if the PKU diet is not controlled properly. Also, in terms of cost effectiveness, if the woman does not control her diet properly in pregnancy, she is likely to have a disabled baby which would require a lot of treatment and care throughout their whole life which would cost the NHS significantly more money

Q10. I think NICE should recommend women trying to conceive and during pregnancy and breast feeding period to be given Kuvan as a basic human right to protect both the mother and unborn child.

Q11. I would plead with NICE to allow women going through pregnancy to be allowed Kuvan. I have hope and dreamed my whole life to start my own family one day and more than anything you would want a healthy baby and to be healthy yourself. Knowing that the PKU diet can threaten those things, is truly terrifying. It puts so much pressure on you as a mother to control your Phe levels, and if the baby is disabled when born. You would have eternal guilt for your child, and your partner, and always feel like it's your own fault. It may increase risk of post partum depression also.

Q12. Yes. I feel that having a child with disabilities, due to a poorly controlled PKU diet, would be much more costly than the treatment of Kuvan itself. And surely it is better to prevent a child from being disabled, rather than pay to support it once the poor child has already been born with mental/physical health issues? It seems unfair and inhumaine

Q13. I plead with you to consider Kuvan for all adults. It would quite literally be life changing. The NHS happily funds billions of pounds for people with obesity or smoking related issues, and most of the time that is self inflicted. PKU is not a choice, I have wished my entire life to just be normal. Kuvan could potentially give that to me, and make my dreams come true. Also please consider the fact that Kuvan is only effective in 30% of people. So it won't be the entire PKU population you will have to fund it for. But for those 30% of people, it truly will be a life changing miracle. Something I have honestly wished for my entire life.

Respondent 3

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. When teenagers get to 18 it is even more difficult for them Tom and go out with friends when they are on a very reduced diet. Some even stop sticking to diet so they can fit in!

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. If my daughter has high levels she is weak and lethargic.

Q6. *[no response given to this question]*

Q7. *[no response given to this question]*

Q8. Whenever we have traveled we have had extra bags to carry supplements etc.

Q9. *[no response given to this question]*

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. My daughter has two beautiful children but had to have approval from her dietitian and specialist as it was thought that high levels in the beginning of pregnancy could cause deformation

Q13. Surely to give Kuvan to everyone would cost less in the long run as people would not need all the other low protein foods that are needed to help supplement the diet!

Respondent 4

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. This is frankly a ludicrous position to take. Do they truly believe that someone's genetically inherited condition stops being a problem when they turn 18? Of course it doesn't! There is no suitable or appropriate justification to allow someone to have access to this potentially life changing drug as a child, only to remove that benefit when they turn 18. My own experience growing up was that during my teenage years and 20's, just as I was finding my independence and left home for university, was when I was least able to be compliant with the PKU treatment (diet). As a result of my lacking the ability to have the good practise and sensibility to comply fully with the diet, my levels were far in excess of the recommended guideline amounts. I also truly believe that the A-Level and Undergraduate degree results that I was able to achieve were severely impacted by my reduced cognitive ability at this point in my life. As a mature adult (36) I now have the sense to follow my diet as best as I reasonably can and still struggle to achieve blood phenylalanine levels within the recommended guidelines. The proposed limit of 18years are completely farcical.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. My own experience is that my own mental state including day to day cognitive ability and mental health are very much influenced by my phenylalanine (phe) levels. There are studies which identify that PKU patients score more highly in terms of being at risk for suffering from mental health conditions such as depression. Anecdotally I have first hand experience of this having suffered more than one bout of severe depression requiring medical intervention in my life.

Q5. High phe levels do very much Impede my decision making, stress levels and mental acuity. I have suffered from depression requiring medication on several occasions. I also find that when I have very high levels I am not always aware of my altered state which makes it very difficult to remain compliant with the diet leading to a catch 22 situation and downward spiral which it can be very difficult to get out of. Often the only way to get out of a situation like this is with the intervention of family members who are aware of my situation.

Q6. There is not enough data on aged PKU patients for this to be able to be true. Nice seriously need to review this policy as poorly managed adult pku patients will end up needing other kinds of support down the line. Reference my comments previously about the risk of serious mental health conditions as a single example. PKU patients can often find that the low protein foods available to them on the diet are very calorie rich, this makes it increasingly difficult to maintain a healthy body weight.

Q7. I have struggled with depression in the past requiring therapy, months off work and medication. All at the expense of the NHS. To not consider these costs is simply an example of willingly and deliberately ignoring the costs to present a false view of the situation. I have in the past also suffered with severe indigestion directly attributed to the supplements i have to take as well as regular migraines relating to high phe levels again all requiring medication and treatment.

Q8. PKU children essentially require round the clock care from their parents/carers to
Make sure they are following the Dickensian treatment that currently exists under the NHS. This should be taken into account as the effect of this can take its toll on carers which may manifest in poor or ill health of the carer.

Q9. This is highly unfair considering that only a small percentage of the adult PKU population will actually be responders to the drug anyway. All PKU patients are at risk of a level of cognitive impairment when following the diet treatment, this burden could be reduced my making the drug available to all patients that are responders - the very people they are excluding are the people that need it most.

Q10. All responders should be allowed to have the drug

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. There is such a small population of people with PKU, and such a small subset of this cohort that will actually respond to the drug, it is beyond me how NICE have recommended to only allow under 18’s to access the drug. To give someone the life
Changing medicine they need to potentially live a normal life, then remove that provision at a point in their life when they need it most is quite frankly inhuman.

Respondent 5

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. It would be unfair to allow children to become used to living with the enormous advantage to their way of life that Kuvan will benefit them with, and then for it to be snatched away from them upon reaching their 18th birthday.

Q3. I do not agree with NICE's view;Apart from there still being a degree of potential brain damage in adults with PKU, they also suffer from significant effects of severe mood-swings as a result of their erratically managed protein consumption.

Q4. *[no response given to this question]*

Q5. My grandson has PKU and suffers from mood-swings, tiredness and lack of concentration, when his blood Phe levels rise above normal.

Q6. My grandson has PKU and suffers from mood-swings, tiredness and lack of concentration, when his blood Phe levels rise above normal. This affects his learning ability, and will consequently have a negative impact on his desirability with future potential employers.

Q7. My daughter is a full time carer for her son, who suffers from PKU. Managing his health, well-being and diet has a significant impact on her mental well-being and ability to earn an income as a result.

Q8. My daughter is a full time carer for her son, who suffers from PKU. Managing his health, well-being and diet has a significant impact on her mental well-being and ability to earn an income as a result. It has brought her once flourishing full-time career to an abrupt stop!

Q9. I believe that NICE have not properly considered the impact of their decision, on the basis of it being discriminatory in respect of both ‘age’ and ‘disability’.

Q10. No comment.

Q11. No comment.

Q12. No comment.

Q13. No further comment.

Respondent 6

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Why would you stop medical support for a life long condition at 18? The treatment will encourage and support adherence and then remove this support at a critical point of development.

Q3. I do not agree with NICE's view; NICE's statements are contradictory

Q4. So many friends in the community have experienced poor mental health, shakes, low bone density as a result of being off diet as an adult. Brain fog is another issue that is constantly being raised. This has led to some people losing employment, relationships etc.

Q5. No, that is accurate

Q6. I strongly disagree that low/high figures in adults hould no be taken into account. I believe that adults largely go off diet and lack support from services. I also believe that as the PIP criteria is so narrow, that adults with this condition are wrongly denied financial support to manage this awful condition.

Q7. I used to spend £60 a month on digestive enzymes for my daughters as the supplements are not only disgusting in taste and smell, but they also cause significant problems with their guts. They have been under a gastro consultant for nearly 8 years.

Q8. *[no response given to this question]*

Q9. No I do not think NICE are considering a fair approach to treating adults.

Q10. Women really struggle to manage their PKU during pregnancy. There are many examples on social media of children born with LDs and disfigurement as a direct result of uncontrolled PKU during pregnancy.

Q11. I am petrified about my children reaching child bearing age for this very reason. Provide appropriate treatment to all who have this life long condition! What would you want for your children and lived ones?!

Q12. NICE should take into account these costs!

Q13. This community deserve to have access to a drug that has been available in other countries for YEARS. Turkey prescribe it to their citizens. Turkey! It is a national disgrace to have had treatment options and not provide these to our community.

Respondent 7

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I think it's a terrible idea, I was taken off diet as a teenager as I was informed it was the right thing to do, but I suffered greatly with mental health issues which I was unaware was caused by pku, and it was only when I went back on diet that things turned around however 50% of my week are bad days as I find the diet extremely difficult.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. NICE must read the studies involving pkus connection to parkinsonism and dementia, there is a clear connection and the diet alone isn't enough to prevent this as there is still high amounts of phenylalanine going to the brain. Also NICE must look into the fact that high levels can be caused by illness this can't be controlled by diet but kuvan would eliminate this issue, being in a calorie deficit will also have a huge effect.

Q5. High phe levels cause me to have mood swings, depression, anxiety and stress, and when levels are high the simplist tasks become difficult I can become extremely forgetful and will misplace things (dementia symptoms)

Q6. Having high levels massively affects how I would go about my life, I would not be able to do my job correctly, I would avoid social events with friends and relatives it would cause problems at home as I can become extremely moody when my levels are high. My life would fall apart.

Q7. I have been seen at hospital for mental health which is a cost that could be eliminated for the NHS also the cost of prescribed foods are also a cost that could disappear.

Q8. Pku has a huge impact on my family, my partner does struggle with it not only does it ware me down it also wares her down which is horrible to see, I question why she continues as it is a burden on her not only food management and shopping but the symptoms I display.

Q9. NICE have not considered treating people fairly at all it's nothing but discrimination everyone should be treated fairly.

Q10. They should make it available to ensure the safety of the unborn child.

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. In my opinion this is age discrimination and the fact that this goes on in the NHS is appalling, you can't treat people this way, those children who are given kuvan will have a extremely difficult time when it's taken away from them, NICE are basically giving them a chance to make something of themselves and be the best they can be and then take it away from them during the most important part of their lives, and they will be hit with this new diet that is so extremely difficult to manage along with a wave of mental health problems they have never experienced that ALL pku sufferers have to deal with. NICE are discriminating against people of a certain age and this has to stop all pku sufferers must be given kuvan to help them progress and enjoy life, we never asked for this condition and we all need help.

Respondent 8

Q1. I agree completely with this recommendation

Q2. I think it is a good idea as I myself find it very difficult to manage dietary treatment.

Q3. NICE's statements are contradictory

Q4. no

Q5. I don't notice the difference of high Phenylalanine levels.

Q6. no

Q7. I don't really have any health issues related to PKU

Q8. I do think nice should take into account the impact of PKU on other family members.

Q9. I think that nice has considered treating people fairly, yes.

Q10. I think they should recommend kuvan to help women manage the risk of maternal PKU

Q11. I do not have any comments or evidence to give to nice

Q12. I do not have any comment

Q13. I would like NICE to take into consideration the affect of PKU on unborn children

Respondent 9

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I find it very difficult to process how this could be a sensible proposal . As a PKU sufferer myself and having a PKU child myself I cannot imagine it would be kind of me to allow my son to access Kuvan and then withdraw this from him in adulthood. There would need to be a consideration whether this would be a good option as a child as he would become used to tastes etc that he could not continue into adulthood. It seems this would be unkind to offer my child knowing that he would then potentially struggle to maintain good levels into adult hood having had his food choices massively reduced . Teenagers years are so difficult with PkU and that is when I went off the rails . I struggled adhering to the restricted diet as having classic PKU my choices were so very limited and once I fell off the diet I have never managed to regain the control to have good levels into adult hood. There are so many issues in adult hood that relate to poor dietary management and i think there has to be arguement that the allowance of kuvan with adults would reduce costs in other areas such as mental health issues which are massively affected by poor levels

Q3. I agree with NICE's view that there is no risk of long term brain damage in people with PKU aged over 18;I do not agree with NICE's view

Q4. My family all have PKU and I think it is interesting to see how the blood levels affect the functionality of us adults when our levels are not being managed well . My husband has had an unexplained subarachnoid brain haemorrhage and although this cannot be directly related to high levels in PKU it also can not be ruled out either . He is now on long term sertraline . He was a child who was advised he could come off diet at 16 and has done so in a big way but suffers with mental health issues etc and massive health anxiety as there is an unknown factor with PKU.

Q5. My husband with PKU has many classics symptoms of high levels and would never be able to get the levels to where they need to be . He and I are first generation Pkus and were allowed to come off at an early age . This has had led to issues such as panic , health anxiety , depression and a general fear of future issues as a result of pku .

Q6. *[no response given to this question]*

Q7. We live with mental health issues and as such are reliant on anti depressants . We have had kidney issues which have required hospitalisation . The costs of PKU are not only dietary aids but also many other issues that result from this .

Q8. Pku not only affects us as the patient but the family around . Having been managed well by my family as a child there is a lot of stress and anxiety caused by High levels in adulthood and indeed the unknown aspect of the future as I grow up . Anyone who deals with PKU has a stress that goes with it as is a Constant . This is the unknown fear and the severity of the impact of high levels regarding daily functionality

Q9. My brother has learning difficulties and struggles to understand his PKU therefore requires so much more support than an adult of a similar age with a higher level of intellect . The impact of this on the wider family means that he has to be looked after even though his level of function is not so bad

Q10. Women who want to have a child who have PKU have control taken away from them . It is imperative that someone with pku has low levels prior to the conception which in the event of decreased fertility makes dietary adherence so difficult . I Had many issues though out the pregnancy and even at zero exchanges could not manage my levels as low as they needed to be even though my level of effort and constant Adherance was exceptional . The stress to my baby and myself was absolutely cropping as nothing more could be done to help me achieve those low levels.

Q11. *[no response given to this question]*

Q12. High phe levels can result in children with developmental delay and it is vital that levels are kept low regardless of what is going on .. kuvan would prove vital in keeping the baby safe in this Scenario

Q13. To offer this to children only is of no help as at some point the luxury of being less restricted will be removed and then they will be required to manage their requirements going forward . This will breed resentment and anger in many which will mean that the chances of managing the diet well in adulthood will be severely depleted .

Respondent 10

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I feel like it must be hard for people above 18 and that they deserve this treatment as much as me or anyone under 18

Q3. I do not agree with NICE's view

Q4. no

Q5. it messes my life up like sleep schedule and increases anger

Q6. yes it can effect your future as it can lessen IQ

Q7. possibly as I do not know any to my knowledge

Q8. I cannot say as its not hard for me

Q9. I don't really know but people should be treated differently

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. help adults

Respondent 11

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. This would change my life having kuvan available. I understand that it is a costly drug however for someone with PKU this drug would eliminate more than just high blood levels. Anxiety and depression are just a few ti mention. I bet nobody in NICE has PKU? If they did they would understand what a hard and derogatory condition it is.
I dont quiet understand giving it to a child then at 18 taking them off it? How hard must that be for an 18year old to have a massive life change for worse? Surely it should be a privilege that when you get to 18 and your brain is developed Kuvan can be introduced into your diet to maintain a healthy and well balanced adult lifestyle? I understand it is difficult to get children to drink their supplements etc however its just as hard for adults- this never goes away!!!!

Q3. I do not agree with NICE's view

Q4. *[no response given to this question]*

Q5. Brain fog is legitimate!!!! I woop out of conversation all the time and I can be quite forgetful on something somebody has just told me.
I constantly feel tired and I am deficient in many vitamins so fatigue and exhaustion is real and it can be a major struggle

Q6. I was off diet for 10 years. I appreciate i don't have brain damage however I suffered chronic headaches and the fear, anxiety and depression I suffered as a result of me not being on a low protein diet were awful I would wish pain like that on anyone. This was due ti be me being in a 'normal diet consuming high levels of phe - So YES high levels of phe can definitely contribute to health
It does make me laugh these questions - if someone in NICE had this i bet this would be a different story. It infuriating having ti fight for something that would literally change your life, and trying to explain to people without the condition how much of an inconvenience it is -you will never understand !!!

Q7. I honestly don't feel that all depression is cause by PKU however it can be a causing factor. I dont see why we should be treated unfairly to anyone else everyone is different so not everyone will suffer in the same way

Q8. The guilt is one of the major things. My mum having ti say NO to everything as a child cause my mum depression seeing me so sad and in the 90s PKU is nowhere where it is today. My family have spent countless hours trying ti make me food I will enjoy and that if free for me to not like anything. The constant battle they had with me and the feeling of worthlessness.

Q9. No again NICE havnt considered treating people fairly. I would love to have the chance to have a child one day but I fear because of how hard its going to be to maintain a low protein diet. I dont see why if there is a something that potentially help and assist me through pregnancy why we are not able to have the chance to have the support of Kuvan to have a child.
Cost is the major barrier here, so obviously something needs to be done to make it easier to get hold of and accessible for all making it fair across the board.

Q10. *[no response given to this question]*

Q11. I would love to try for a baby one day. I have massive anxiety that I won't be able to come trol my diet to be able to deliver a healthy baby. Also if I had a baby and there was something wrong with them because of something I ate or something that made my levels sky rocket during pregnancy I would NEVER forgive myself. I want to have a chance to have a chance to have a baby just like anyone else.

Q12. *[no response given to this question]*

Q13. I would like you to consider people and actually pur yourselves in our shoes and imagine how much of a difference it would make to you. Cheaper alternatives need to be found or bigger budgets- this would mean so much to SO many people.

Respondent 12

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I do not agree with letting children take it and then stop. This will encourage poor diet behaviour exactly when they need to have more control. Children are becoming more independent at this age. This is inappropriate and potentially dangerous. My husband thinks this is the worst time to make a change in the diet.

Q3. I do not agree with NICE's view; NICE's statements are contradictory; I have worked with people with brain injury. I do not think the brain is ever at a point where it cannot be damaged. My husband has PKU. I have seen a deterioriation in his symptoms as get older.

Q4. My husband is 51 and came off diet aged 16. His condition deterioriated over time whilst his levels were uncontrolled. He was very tired all the time, had low mood, was snappy and emotional. He was very forgetful and could not complete basic tasks in the house. His symptoms have have improved after returning to diet but he still struggle with daily functioning.

Q5. I agree with the statement about the affect of high phe. High phe also has an impact on others in the family. High phe affects my husband's ability to function and other members of the family have to compensate for his deficits.

Q6. High phe in the past will affect you in the future. You will not fully recover your brain function. My husband has returned to diet but he has not achieved a normal level of functioning. He has more energy. I believe the years off diet has impacted him permanently. My husband has a brain injury - slow processing speed and impaired functioning.

Q7. My husband has terrible dental problems relating to PKU diet. He has low bone density. He has low B12. I am worried about higher risks of Parkinsons and brain related issues. I am worried about the future impact on his health. My husband is at the older range of early treated PKU patients and their future is not known.

Q8. PKU has a massive impact on everyone around him. My husband has cognitive impairments. He needs reminding and help with his PKU treatment and with everyday tasks. Living with PKU affects everyone's activities, where we can go and what we can do. My husband's mum is retired but still cooks PKU meals for him as he can't do this himself. I have to help manage my husband's treatment and have to compensate for his deficits in functioning. He has memory problems. He does not manage risks or plan well and can need supervising.

Q9. I disagree with NICE's approach. From my own experience, people that have cognitive problems will need a support network to manage their diet. PKU is very complicated and if you have cognitive problems you will struggle. If my husband did not have this family support his functioning would be a lot worse. We buy extra food to help him stay on diet. If people do not have a stable level of phe, you can have a downward spiral, where you lose your job, can have no income, less family support. This would mean people would be in an even worse position and more vulnerable. It is not right to leave people without treatment. People with PKU need more support.

Q10. More support is needed for pregnant women with PKU.

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 13

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. As a mother to a young infant with PKU I am already aware of the extraordinary amount of care, planning and management that goes into the low protein diet. It is extremely complex and time consuming, and yet I am coming to it as an adult with a good knowledge of food and cooking. To place this burden on a person at the age of 18 - when they may be taking exams, starting university, leaving home, starting a new job - is reckless and will undoubtedly create a crisis for teenagers and young adults. Not least the impact of going through their teens knowing that their life changing drug will be denied them as of their 18th birthday. PKU does not change at the age of 18, so there is no reasonable justification for removing treatment at this age.

Q3. NICE's statements are contradictory

Q4. Putting anyone at risk of brain injury is reckless and discriminatory. In saving money by denying deserving adults the treatment they need you are creating a cost burden in mental health, other physical and psychological health impacts and to other government agencies - ie the cost of people unable to work and requiring lifelong additional care.

Q5. Although my daughter is very young and I am managing her diet well, the risk of high Phe levels is an ever present underlying worry. This worry will not go away when she's 18. I fear for her desire to become a mother herself and NICE's decision to ignore the extremely high risk needs of maternal PKU syndrome is very likely to impact on her. You are therefore creating a gender imbalance by discriminating against adults and denying them treatment. Your decision may have a direct impact on whether my daughter can safety try to have a baby.

Q6. NICE has oversimplified the impact of living with high or low phe levels. It is more than 'brain fog'; it effects a person's ability to work, socialise, cope with normal every day circumstances most people take for granted.

Q7. NICE is creating a longer term health crisis for people with PKU by denying the treatment to people over the age of 18. The full effects of a lifetime diet of synthetic protein and low natural protein intake is not yet known. NICE is risking the health of our children by denying treatment that could allow them to follow a healthier diet and forcing them to live on a high sugar diet of processed foods. As well as the mental health disorders that can lead from PKU (both people on diet who suffer from social isolation and those off diet who suffer from anxiety and depression due to uncontrolled phe levels) and the physical affects, there is an issue with oral health due to the high sugar nature of the three or four times daily intake of protein supplements.

Q8. As a mum to a 1 year old with PKU I can tell you this is a complex and restrictive diet that requires an advanced knowledge of food and cooking to even come close to providing appetising and enjoyable food. On top of caring for a 1 year old I spend a lot of time looking for appropriate recipes, looking at how they could be modified, following various low-protein recipes, buying (expensive) special ingredients, preparing food for her for nursery (because the kitchen can't supply her with a suitable diet). I am a devoted mother and will do everything to keep my daughter's PKU under control for as long as she'll need and accept my help. But I can't work more than 2 days a week and can't see myself being able to work full-time all the while I'm managing her diet. I have only one child and don't know how I would manage the needs of another child while managing the diet for my daughter. If my daughter decides to have children herself I can't begin to imagine how hard it would be for her to

manage her own very restrictive diet comprehensively whilst also caring for her children. As I said before, this is a discriminatory decision not just based on age but also on gender because the burden of care falls on women in the vast majority of homes. This means women with PKU are managing their own diet as well as their own household and children. This means even parents of adult children with PKU with additional care needs - this burden will fall on the mothers. Have you run an Equality Impact Assessment on this decision? Or on the treatment of PKU in general? I doubt it.

Q9. The NICE decision not to recommend Kuvan to any adult over the age of 18 has shown a complete lack of true understanding of the illness and the nature of dietary treatment. As a well educated woman in a well-off household, with a good understanding of food and cooking I am still finding the diet hard to manage. To place this burden unnecessarily on more vulnerable groups is unthinkable and if the committee making this decision really understood PKU, it would be impossible for them to deny treatment to everyone who needs it. Having PKU is for life and it affects every sufferer in different ways.

Q10. NICE needs to recommend Kuvan for all adults over 18 who respond to it. There is enough evidence to suggest that the needs of the unborn child to a mother who has PKU are great enough to warrant that the mother receives the necessary treatment. The current guidance for treatment of maternal PKU is absurd and it has been acknowledged that it is wrong. Having to prove that you can't stay on diet (huge risk to the unborn child) while you are pregnant is a case of setting fire to the building to see if it's fireproof. Undo this dangerously reckless decision and make Kuvan accessible to everyone who will benefit from it, including the unborn children of woman with PKU.

Q11. As a woman who suffered years of infertility and several miscarriages before having my daughter, I find it unbelievable that you can consider withholding this drug from women who are trying to conceive. I know from my own trauma that pregnancy doesn't always go according to plan. If I had PKU I would have been on the intolerably restrictive pre-con diet for over 3 years before becoming pregnant with my daughter. NICE needs to recommend Kuvan for all adults over 18 who respond to it. There is enough evidence to suggest that the needs of the unborn child to a mother who has PKU are great enough to warrant that the mother receives the necessary treatment. The current guidance for treatment of maternal PKU is absurd and it has been acknowledged that it is wrong. Having to prove that you can't stay on diet (huge risk to the unborn child) while you are pregnant is a case of setting fire to the building to see if it's fireproof. Undo this dangerously reckless decision and make Kuvan accessible to everyone who will benefit from it, including the unborn children of woman with PKU, including the women who are hoping to get pregnant and bring a healthy baby home.

Q12. The cost calculations in the summary and discussion are very clearly flawed and shouldn't be admissable as part of the decision. The decision ignores all the indirect costs of uncontrolled PKU and this is a primary example of such a thing.

Q13. My daughter is just about to turn 1. Finding out she had PKU when she was less than a fortnight old was one of the most terrifying things I've ever been through. She is a much loved, beautiful, bright, funny little girl. I am doing everything I can to manage her phe levels and keep her diet as varied as possible. It is not easy and takes a huge amount of thought, research, planning and food preparation. As she gets older this will become harder and harder to do. Not just because her appetite will grow as she gets bigger, but she'll become more aware of her difference. She'll be aware of a whole world of food that she can't eat, she may feel excluded, embarrassed by her difference. She'll almost certainly find herself in situations where her diet isn't catered for, so she has a choice to go hungry or eat something that she knows will do her damage. What kind of a choice is that to make?

To put this into context, think about what you've had for breakfast today. Cereal with milk? Porridge? Toast? Maybe fruit and yoghurt. Did you have tea or coffee with milk? If you've had a piece of ordinary sliced bread today then you've already exceeded the amount of protein my daughter will be able to eat in one day. If you've had a normal adult size portion of cereal with milk then you've probably exceeded it two or three times over. That means for the rest of the day nothing with any traceable amount of protein in. So no bread, no milk in your tea or coffee, absolutely no meat, fish, eggs or cheese. But that's ok because you can select vegan options instead, right? Except for anything containing beans, lentils, nuts, tofu or anything that uses wheat flour of any description. You can probably make a decent meal using veg though – but you've already exceeded the amount of protein you can eat in a day, so that means no potatoes, no peas, no broccoli or cauliflower, no sweetcorn.

What have you got planned for lunch? Maybe you'll just run out and grab a sandwich or something from M&S if you're in a hurry. Afterall if you have a demanding job and active life outside of work when would you have time to plan (and make) every single meal in advance? Except M&S doesn't stock sandwiches made from low protein bread (no one does).

Imagine there's a special occasion coming up, perhaps it's your birthday. The perfect chance to go out for a meal with loved ones. Surely if you just tell the chef you have PKU they'll be able to whip up something with the right level of protein for you. Well, given that only 1 in 12,000 people in the UK have PKU it's highly unlikely the chef will have heard of it, let alone catered for someone with it. Well you can do lots of research and find a vegan restaurant, make sure they have suitable dishes that don't contain all the vegan proteins you can't eat, maybe phone ahead to let them know and arrange something suitable for you to eat. Most people just phone ahead to book a table.

Perhaps it's someone else's birthday, in which case in all likelihood there'll be nothing suitable for you to eat so you'll either sit there watching everyone else eat or perhaps just give it a miss.

Easter's coming up too, so maybe your nursery/school/workplace will be providing some chocolatey treats. Which of course you can't eat because chocolate is off the menu. If they're really forward thinking they might include some vegan treats, but you'll need to see the ingredients and food label to check if you can eat it and then do the necessary calculations to measure out exactly how much you can eat within the constraints of your daily allowance.

In fact, can you think of any celebration that doesn't revolve around food? There aren't many.

Well holidays, at least, are a good time to let your hair down and enjoy yourself. As long as you've researched the location you're staying at and have identified the restaurants that will be able to cater for your extremely strict dietary needs. And provided you've been in contact with the people who supply your medication to make sure you have enough of it to see you through the duration of the trip. And provided you can pack your prescription supplement and your prescription food and your clothes, toiletries, and so on without incurring a hefty excess luggage bill.

There is never, ever a holiday from PKU. For people like my daughter every single day and meal has to be planned in advance. It might not sound like much but as a mother caring for a nearly 1 year old who has this condition, I can tell you that managing this diet is not easy and we are only at the beginning of this lifelong journey.

The idea that the one drug treatment is not considered ‘cost effective’ enough to fund for all people who would benefit from it is truly absurd. The idea that you can consider prescribing it up to the age of 18 and then expect an 18 year old to suddenly be plunged back into the grip of an extremely hard to manage diet – at a time when they may be sitting exams, starting new jobs, starting University, moving out of home for the first time, trying to set their lives up - is unbelievably cruel. This decision is at best misguided and at worst reckless. How can we possibly consider our health service to be world class when an effective drug treatment is denied to sufferers in this country, even though it’s available in most others?

This decision by NICE is wrong. They must do the right thing and approve Saptopterin for everyone who can benefit from it. They must stop ignoring the hundreds of voices who are telling them that suffering from PKU – at any age – is a huge struggle that affects every area of their lives. They must not invalidate their experience by saying that living with PKU does not significantly affect quality of life enough to justify the cost of a drug that could alleviate their daily struggle. PKU does not go away at the age of 18, and for NICE to declare that the quality of life of someone suffering from it is not compromised enough to warrant them funding the only medical treatment that’s available globally for it is only about money.

You must overturn this decision. You must pave the way for the next treatment for PKU that comes available and may help every single sufferer. If you declare that quality of life of the over 18s isn't valuable enough to be worth saving then this will trickle down to the next consultation for the next PKU wonder drug.

There are so many other aspects to PKU than just an unbelievably restrictive diet. The physical and emotional side effects of the diet itself are one; the physical and emotional side effects of being unable to stay ‘on diet’ is another. There's so much more to it on top of trying to manage an extremely hard to manage diet.

Respondent 14

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. This proposal is not accept le in my opinion. There is no evidence known to medicine that suggest the brain stops development at 18. In fact there is plenty of evidence to suggest that neuron development and expanse goes way into adult years, well beoyind the age of 18. Giving a paintient a treatment option and then withdrawing it based on age is not ethically acceptable and never before has this been done. Although some (mainly one individual) have suggested there is no negative impact on brain function when withdrawing dietary treatment after 18, Nice have for some reason ignored plenty of evidence and first hand patient accounts of the negative impact of withdrawal from diet in their adult years. The proposal seems to be weighed by a single opinion of one individual in the field of PKU, which in all honesty is quite ludicrous. It is hugely dissapointing that a potential treatment option can be provided to a child only for them to have to have it taken away when they turn 18. It is my fear also that children who respond to kuvan will not have developed the necessary skill set to sufmddenly follow a strict pku diet when they turn 18 and the psychological impact this would have on any individual would be detemrenental to their well being. It is simply not acceptable and would also open the flood gates for litigation down the line.

Q3. NICE's statements are contradictory;Any person who reads this section will find the absolute contradiction between the two statements. I think Nice should be embarrassed that they actually stated both these comments and feel it is acceptable given the severity of the potential outcomes when treatment is withdrawn.

Q4. *[no response given to this question]*

Q5. *[no response given to this question]*

Q6. *[no response given to this question]*

Q7. *[no response given to this question]*

Q8. *[no response given to this question]*

Q9. *[no response given to this question]*

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 15

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I struggled, and still do as an adult, to control my diet growing up, it’s not just about not being able to eat certain foods, it’s a fight about mental & physical health

Q3. NICE's statements are contradictory

Q4. I can tell so easily even now as a 22 year old adult that when I consume to much protein it affects my brain activity, depression, processing issues, loss of memory etc.

Q5. Same answer as above, as well as leading to making bad decisions and not responding in reasonable ways

Q6. Yes, I wish I had the opportunity to perform better in education; concentration, calculations etc. As well as I go through stages of weight loss

Q7. Yes, I have to pay extra for free from, vegan, vegetarian options, all of which are very touch and go anyway - I could pay for prescription food but the quality is decreased. My main issue is weight loss and being able to control my weight, I have a high metabolism as it is, having to control my diet makes it so hard to increase weight.

Q8. Yes - extra costs in having to find additional meals for PKU children, as well as the mental impact when PHE levels are up

Q9. I can not give opinion as not in position but no I do not think they are treating fairly.

Q10. Tests

Q11. N/A

Q12. N/A

Q13. Kuvan could be life changing to so many people, please re consider

Respondent 16

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. The whole point of kuvan is to allow phenylalanine levels in the blood stream to be low, enabling a better diet and outlook for the person. To stop this at 18 is ridiculous. I myself came off diet toward my late teens and have had issues because of it. To actually stop it at 18 would mean that their diet would be incredibly restricted and they wouldn't have had the experience of a restricted PKU diet. This means that their health will suffer. It is a life long illness and a unavoidable lifestyle.

Q3. I do not agree with NICE's view

Q4. I myself have recently started on the PKU diet after years of being off it. When I wasn't on diet, my reaction times were slowed, my speech patterns off and I found it harder to concentrate and perform everyday tasks sometimes. Phenylalanine in the blood attacks the body, which is the reason why it is necessary for the diet in the first place. I actually cannot believe that NICE would even entertain the possibility of stopping the diet in adults when it's been proven effective. Not to mention that I struggled with my diet for years, trying to figure out what I could eat and couldn't. Not to mention that growing up avoiding certain foods due to protein content means the likelihood of these 18 not knowing what to eat and what not to eat. Not to mention balancing nutrional needs if they come off diet, the dietary substitutes had what they needed at a young age. No diet surely means no protein substitutites which means if they stick to a low protein diet, they won't eat foods with the necessary vitamins and minerals such are red meat for iron and the like.

Q5. As stated before, high Phe levels affect my reaction times, speech patters and have a significant effect on my mental health. Going back onto my diet has made me realise how terrible I felt and how much better I feel now.

Q6. Having high levels as a child meant I found I was more susceptible to illness, low mood and poor concentration. This in turn caused purchase of over the counter medication, time off school and work which obviously causes issue.

Q7. PKU diets being restrictive means having to buy food specially to ensure compliance with the diet. Having to go good shopping for specific items, having to buy more expensive food such as vegetarian options cost more. Prescriptions as an adult cost meaning food has to be paid for as a prescription or a prepayment certificate is needed. This has affected me at the moment being unemployed and trying to ensure I have access to food I am able to eat. This has been a challenge at the moment.

Q8. PKU children have to have their food weighed. Food has to be bought specially for their consumption. Parents have to watch their children's intake vigilantly. This even means having to educate other parents that their children visit so that they are aware of what can and can't be given. When eating out they have to ensure any restaurant or place to eat and made aware of the issues and meals are changed to allow for the restrictions. Children also have to take their protein substitutes and keep track of when they are meant to have them. This means parents are responsible for this until the child is mature enough to understand why it is necessary and important. This also means when traveling, the parents must take into account bringing medication with them, allowing for any weight restrictions if travelling abroad and necessary certificates to allow travel go medication.

Q9. I don't have any complications as stated thankfully, but I can fully understand how hard it would be. I myself sometimes forget how many protein substitutes I have taken in a day, or how many points of protein I have left for a day

Q10. Women with PKU are told to watch their protein intake to ensure a good pregnancy. Why would this not be recommended for those women to ensure a healthy pregnancy?

Q11. I am not female so thankfully I never have to have this concern.

Q12. PKU has been proven when untreated to cause neurological issues which require monitoring and health care assistance.

Q13. I can't believe NICE hasn't taken into consideration the consequences of taking away treatment from patients who would benefit from it. That PKU is a life long condition that doesn't end after 18. I am appalled by their lack of insight. I suggest NICE actually speak to PKU patients first hand to understand the problems faced, rather than than gues based on statistical analysis

Respondent 17

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. PKU doesn't just vanish after a patient turns 18, it makes no logical sense. Have these people even been educated? I have developed bi-polar disorder after teenage years and have recently diagnosed with intercranial hypertension that has effected my brain. I have more white matter than I should and all of these things were diagnosed when I was 24. Therefore, they continuously developed from a teenager, through my early twenties, and still effect me now. PKU is a lifelong condition and there is likely going to be more mental health conditions caused by such a huge sociological change that would actually cost the NHS more than prescribing it to those who respond into their adulthood. Think about the CET/PET brain scans I had (and the ones I will have every 5 years from now) and how much they cost compared to a diet on Kuavn. What costs more I wonder... I can't manage my diet. I am in psychodynamic therapy and have been for the last 18 months. I am on daily bi-polar medication. A lot of PKU people are like this way into their adulthood. Mental health problems from poor diet management can happen at any point in a person's life time. Restricting a child who has grown up with the privledge of a lax diet will cause more problems, not less. My health costs could have been drastically lower if I had been introduced to Kuvan and stayed on it. I have irreparably damaged friendships, relationships, and my familial support because of my brain damage, brain damage I still inflict on myself because I have trouble sticking to my highly restrictive diet. My bi-polar disorder will always be with me but it may ease if I am able to eat food with Kuvan because my moods won't be effected by the PKU. As a morbidly obese PKU adult i'm at high risk for diabetes, heart disease, and kidney failure as it stands. Being able to eat more protein would enable me to lose weight (believe me I would like to) and prevent other more common health conditions that strain the NHS. I cannot eat protein on the current diet, only carbs. Is it any wonder I'm so fat? On Kuvan I could eat protein and cut carbs hugely changing my BMI, lots of us are like this, I know there isn't a lot of us but we all cost so much money during our entire lives because of the effects of poor diets. These other health costs must be considered. You're costing the NHS more, not less, with these misinformed decisions. Stopping Kuvan at 18 only delays these problems, it doesn't solve them.

Q3. I do not agree with NICE's view

Q4. My white matter is increasing and I continue to have headaches, high intercranial hypertension, long term life long mental health conditions, and my pituitary is irreparably damaged.

Q5. I live in a permanent fog, I constantly misunderstand boundaries and fail to function at work and university the way I am expected to. I have disassociated so much from my body because of my relationship with food and its effect on my body to the point it feels like I'm not alive.

Q6. As I have discussed above that is a reductive view because PKU means that there are constant additional health care costs that keep racking up how much we cost the NHS in my case: bi-polar, diabetes, kidney failure, bladder control, psychodynamic therapy, 5 yearly CET/PET scans and then all of my PKU food and supplements on top of that.

Q7. All have been discussed above

Q8. My family was broken down because of my PKU. There were huge discrepancies in care and control over me. My family hasn't even begun to recover and its 8 years after I left home and I've had extensive therapy. My partner is my primary carer, most of our relationship has turned into a carer/patient relationship, not a sexual relationship, if I could take care of myself and my diet better I wouldn't have this issue.

Q9. Those who have mental health conditions (bi-polar/depression/anorexia)

Q10. Well I'm too scared to have a baby and many other PKU women are because it is terrifying to think about having to control the diet that strictly when we struggle as it is.

Q11. I will never have children unless I have help, I would harm them with how hard it is to keep the diet. I think that has to be some sort of human rights issue at least? Making a person feel like they can't have children when it could be easily rectified? Pretty disgusting.

Q12. Just like all of my above examples, unless you take into consideration all the other costs we have you'll never understand our true cost to the NHS and I thought people want to save money lol

Q13. It's ill informed and the system is broken, it doesn't make sense that people want us to keep draining the NHS. To be fair, why aren't we all on PEGPAL?

Respondent 18

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. To only provide those under 18 is an absolute disgrace, I have had to manage on only 10 exchanges of protein all my adult life, I turn 40 in a few weeks time and the difficulty of managing this diet and trying to live a normal life cannot be understated. I cannot go for meals with friends and family easily or usually at all, I frequently am hungry and the low protein substitutes whilst good are nowhere near the quality of "normal" food. Trying to meet a partner proved to be an exceptionally difficult time having to explain I couldn't go out for meals, a normal thing people would do when dating and this was a very difficult thing to overcome before meeting my now wife.
In addition to provide this drug only until someone reaches 18 then strip it away from them is beyond cruel, they will have got use to something resembling a normal diet potentially then at a time where they are entering a new phase of life, maybe university or entering work you are going to make their lives so much harder is a total disgrace

Q3. I do not agree with NICE's view

Q4. *[no response given to this question]*

Q5. Mood swings and lack of concentration are very noticeable and others in my family notice this in me and I can recognise it in myself, in addition I can be irritable and suffer a lack of patience

Q6. I totally disagree. Cost should not be a factor, the extreme nature of pku and how severely limiting the diet is means people with PKU never experience a normal life and every effort should be made to ease their suffering, this is our only life and we won't get another chance so everything that can be done should be done

Q7. I don't have health issues but when considering the costs it should be noted that I receive multiple PKU supplements which in itself cost the NHS thousands of pounds each year

Q8. Yes, in particular for new parents I know how much my mum suffered and how hard it was for her more should be done to support new parents

Q9. My son has severe autism but fortunately not PKU if he had there is no way he would understand the implications of the diet and this is likely to continue into adulthood so having Kuvan would be vital for him to help keep his phe levels low

Q10. They should just give it to all adults full stop so this wouldn't be an issue

Q11. Give the drug to all adults with PKU

Q12. Give the drug to all adults with PKU

Q13. The proposal is disgraceful and cruel and needs immediately changing to provide the drug to all those with PKU, imagine taking away a diabetics insulin and informing them the only way to manage their condition is with diet, this is the same thing, just because PKU is rarer we have always been ignored but this diet is every bit as difficult to manage as diabetes and the consequences of not following the diet are equally severe

Respondent 19

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I think stopping kuvan at age 18 is a bad idea because being given more of a free reign on what you would eat then having it taken away and be put on such a restricting diet would be extremely difficult for anyone to manage as the diet is so restricting. As someone who has PKU I know first hand how difficult it is to learn to manage the diet on your own, as a teenager, when you have been on diet as a child, so trying to manage the diet by yourself, later in life, with not much previous experience would be even more difficult and in most cases people would not go in the diet. This would cause them to struggle as adults.

Q3. NICE's statements are contradictory

Q4. There may be no evidence, yet, of long term brain damage in adults however through my own experience I know that high Phe levels do affect how I feel and function which are connected to the brain; therefore high phe levels can not be good for the brain short or long term. When I have High phe levels I can not function correctly on a daily basis. I am immensely tired, sleep a lot, extreme brain fog, feel/be sick, agitated, very anxious and poor decision making, and extremely paranoid, which are all symptoms that affect the brain.

Q5. High phe levels effect me in a bad way, but the diet is so restricting and difficult to manage that it is hard not to have high phe levels and then you are just stuck in a cycle of feeling ill but it is such a struggle to not feel this way. I have extremely bad anxiety and am extremely paranoid when I have high phe levels. I get annoyed easily, I'm agitated and get confused easily, at simple things that I usually would find easy to do. If my levels are really high I get hot sweats but I'm not hot in temperature. When I feel any of these it makes it even more difficult to follow the restrictive diet.

Q6. I think having high phe levels can affect your future health because of my own experience. In the past I have had high levels because I have always struggled on the diet, which has definitely effected me now in my life. I have no confidence or self belief and I'm always anxious and paranoid about everything and anything, so I think high phe levels have definitely effected my life experiences.

Q7. Patients with PKU have high healthcare costs for treating PKU and some people have even higher healthcare costs as they have additional health issues which are related to PKU. I have depression and sever anxiety, which are related to high phe levels and struggling with the restrictive diet. These also have to be paid for, as well as prescription foods and supplements to keep on the diet. It also causes stomach problems and severe headaches.

Q8. Yes because it does not just effect the person but also the family. It is difficult for the family to manage a child and adult with pku because it has a massive impact on daily life, which no one would understand unless they lived with it.

Q9. People's situation is irrelevant because pku is such a difficult and restricting diet to follow without considering any other factors. I don't think people have been properly considered to be treated fairly so all pku patients can have a chance at trying to see if kuvan works for them.

Q10. I think they should recommend kuvan to help women manage the risk of maternal pku because if wanting a baby the diet is even more restrictive to lower the chances of harm to the baby. The woman needs to be on the most restrictive and most difficult pku diet to have low phe levels but also make sure the baby gets enough nutrients. This extremely hard to manage and kuvan would definitely help that.

Q11. I struggle to manage my diet now so the thought of ever being able to have a baby and control my phe levels in pregnancy seems impossible without the help of kuvan and it is scary the untold damage that could be done by not restricting yourself.

Q12. I think they should have included costs as this is a really important part of pku

Q13. *[no response given to this question]*

Respondent 20

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I have a 38 year old PKU daughter so long experience of the diet. It is totally unrealistic to expect someone who has grown up using Kuvan to the make a drastic change at 18. They would probably go off diet causing much ill health. You need to grow up with the traditional PKU diet to be able to carry on stomaching it in adulthood.

Q3. NICE's statements are contradictory

Q4. No

Q5. My daughter is very intelligent, absolutely committed to adhering to the diet and generally manages it well but I know she can have periods when she struggles to keep Phe levels as low as she would like and experiences some of these problems along with anxiety and stress in carrying the burden of the diet. You need a high level of self control to keep to the diet.

Q6. No I do not agree levels should be ignored in calculating cost effectiveness for adults. High Phe levels can effect a PKU sufferer at crucial times e.g. at exams or at times of stress at work so it is ridiculous to think the benefits of Kuvan giving more stable Phe levels should not be taken into account.

Q7. My experience is that a PKU is prone to anxiety and stress caused by the burden of living with a strict diet. The diet reduces quality of life - everything has to be well planed, very little opportunity for spontaneity, travelling whether for work or leisure is very difficult, socialising is affected. Together with worries for the future - what are long term health issues. Also day to day there are problems with guts e.g. stomach ache, constipation.

Q8. Yes NICE should consider the wider picture and effect on families. One example I can give is the difficulties in getting child care for a PKU. I always considered my daughter was my top priority and consequently worked only part time when she was very young. It was not possible to get adequate care for her outside the immediate family.

Q9. This statement from NICE does not make sense. These disadvantaged groups need a better treatment even more. It seems NICE are not recommending the treatment for adults because they do not know how to measure the quality of life for PKUs.

Q10. Any PKU patient should at least be able to trial Kuvan and see if they respond to it. Anyone who responds should be able to have it if medically recommended. This should apply equally to women who wish to conceive and need to be especially careful on Phe levels. This again reveals the ignorance of NICE on the PKU condition and is discriminatory towards women.

Q11. I have no comment on this.

Q12. Another flaw in the assessment process.

Q13. I do not think NICE has properly understood PKU and how it affects sufferers' lives. The recommendations seem perverse in the light of the evidence put before them. I appreciate they have to look at costs but given the number of PKU patients is quite small and only a proportion of those would respond to Kuvan I cannot see how cost can be such an issue. Consider how much Type 2 diabetes costs the country - this is a preventable disease - PKU suffers have no choice. NICE should build into their costs a factor to reflect the improved quality of life for those who respond to Kuvan. One factor in living with the burden of PKU is the hope that some treatments will be developed to make the diet less onerous. This outcome from NICE has dashed hopes and will contribute to more anxiety and depression in PKUs.

Respondent 21

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. My daughter has PKU. She's now 21. We've been hoping for Kuvan to be available to her for more than 10 years, but this proposal would not allow her access to it now. Why should she be denied a drug which could dramatically improve her quality of life? Life doesn't stop at 18. Also, why should a child have access to a drug that can dramatically improve their quality of life, then have it taken away on their 18th birthday? Their lives will regress. Their diet will regress. Their mental health will decline.

Q3. NICE's statements are contradictory

Q4. My daughter suffers from cognitive impairment as a result of having PKU. She has always been on diet and has very good control, takes all her supplements as required and keeps a close eye on her levels, however this is clearly not enough to prevent cognitive problems.

Q5. The effects of high Phe levels described here are all true. However, these immediate effects while Phe levels are high are not the only concern. The bigger picture is that over time these effects combine and build up, manifesting themselves in longer-term mental health issues, which have an extreme negative effect on quality of life.

Q6. PKU is for life. The effects of PKU are for life. The challenging symptoms of high and low Phe levels influence a person's whole life and future. The long term, life affecting implications of PKU must be taken into account. In my opinion, anyone – or any organisation – that thinks they should not be taken into account have no compassion and are treating patients with PKU inhumanely.

Q7. My daughter's mental and physical health problems caused by having PKU, have resulted in – and will continue to result in – many hospital appointments, medical consultations and referrals. The medical, physical and psychological problems just 'exist' for her – and despite clinicians best efforts – they are never resolved. They are a way of life for her. All these appointments and consultations, brain scans etc must cost the NHS a lot of money.

Q8. From a practical point of view, PKU is a way of life for patients, family members and carers. And as a result, this way of life has a direct negative impact on quality of life for all concerned. So family members, carers, parents etc are all directly affected by PKU and are also exposed to the potential deterioration of their mental health, just as patients are.

Q9. It seems that NICE have concluded it is too expensive to recommend Kuvan because there are too many groups of adult people who would benefit from it. Surely the fact that so many adults could benefit from a drug is not a reason to deny them it. This is not fair.

Q10. It is well know that there is a particularly high risk with Maternal PKU. High Phe levels and poor control is a significant danger to the unborn child. If the committee is 'not aware' of any evidence that enhanced Phe level control would benefit the unborn child, then could they not consult with experts in that field? Maybe the committee can't quantify this with specific data, but it's common sense. Kuvan should be available to women to manage the risk from Maternal PKU – to improve the outcome for both mother and baby.

Q11. My daughter should have the opportunity to consider having children in the same way as all women of childbearing age who are able to conceive should. Unfortunately this is currently not the case. She should not have to cope with the additional anxieties and worries relating to maternal PKU and it's possible consequences. I know that some women with PKU do not want to take the risk and so decide not to have children. They should not have to make that choice.

Q12. The committee's decision of not recommending Kuvan to adults seems to be very short-sighted on many levels. Putting aside the physical, psychological and ethical reasons, the practical issue of cost is clearly important to consider. A long-term view of effective cost saving would be to consider the ongoing lifetime costs associated with caring for individuals suffering from neurological damage as a result uncontrolled Phe levels in Maternal PKU.

Q13. *[no response given to this question]*

Respondent 22

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Although the diet is generally stricter for under 18s I believe it gets harder to manage and control the strict diet the older you get especially with a physical job and its difficult to find a variety of foods without protein.

Q3. I do not agree with NICE's view

Q4. Even now I am struggling to read and concentrate on what I am writing. It is difficult to remain focused and I struggle with mental health and anxiety and struggle with my emotions

Q5. I regularly struggle with symptoms described and when I was unable to get my supplements for a few weeks I got to a stage I was trying to read something out but I couldn't say the words and this was very scary

Q6. The phe levels have a massive impact on every day adult life from mood swings and inability to concentrate when filling out important forms

Q7. I struggle with anxiety and have been on fluoxetine for over 10 years. I have also been in therapy sessions. I struggle with emotions and often think about self harm which I used to do.

Q8. Going out for meals with family when you cant eat most of the food on the menu can lead to disagreements

Q9. I dont think NICE have considered anyone with PKU and their quality of life just the money aspect

Q10. I think this is awful and the pressure on a pregnant PKU woman is one of the reasons I never want children

Q11. I have avoided sexual relationships all my life due to a fear of pregnancy and having to abort the pregnancy due to irreversible damage to the foetus

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 23

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. As a parent of a teen age son with PKU, I have made financial sacrifices, which effect my family as a whole to self finance Kuvan. My first observation when comparing self funding Kuvan, from a country outside of the EU, as compared with the costings quoted in the technical review ID1475, is high figure quoted for the drug. The list price of sapropterin is £597.22 per 30-tablet pack of Kuvan, from drug manufacturer BioMarin. The actual costs payable by the NHS are discounted by a patient access scheme. As these figures remain confidential then the true stakeholders to this consultation (PKU suffers and their carers) are asked to comment on this process without being privy to all of the information pertaining to the final decision leading on from this review. My suggestion would be to put in place a confidentiality agreement with all stakeholders that express an interest in receiving the costings information and then ask for further consultation with this information in place. Only then can we make informed comment on what is in effect a commercial/financial process. I personally would also be in a position to make a price comparison with purchasing from the same company outside of my country of residence. Further, as it currently stands I would make the observation that the NICE technical appraisal is not fit for purpose in its current form and as such is open to legal challenge. Further NICE have a target QUAL's level of £20,000 per annum and there must be an assumption in the adult calculation that this figure is breached as Kuvan it is not recommended beyond 18. The full calculation should be released and opened to scrutiny as this is money spent by the public purse.

Q3. I do not agree with NICE's view

Q4. In its current form the NICE technical recommendations, i.e. stopping funding for Kuvan at 18, is knowingly putting patients brain development at risk up to the age of 25. Clearly the recommendation should be as a minimum up to the age of 25. The NICE review has stated that a low protein diet in adulthood will result in reversible brain function. For this to happen there needs to an allowance for the time and money it take to shop and prepare for this low protein diet and this calculation is not considered by NICE.

Q5. The process of taking a patients Phe levels is currently a blood sample, normally taken early in the morning and posted to a NHS hospital/lab to under go testing, ultimately generating a Phe result. This process, particularly when interrupted by a weekend can typically take 3 days to a week. There is an anxiety level associated with waiting on a Phe level and then, if higher than anticipated this can lead to further anxiety associated with establishing the reasons behind this unexpected raised Phe result. From observations over the years, in dealing with taking bloods and establishing Phe levels with my son, the incidence of unanticipated raised Phe levels, while on Kuvan are greatly reduced. There have been far less spikes in Phe levels and less reasons to constantly question my son on his diet and this benefit is felt through out the family,

with lower overall stress levels. Thus I dont believe there has been enough weigh placed against the benefit that Kuvan gives a patient in fluctuating Phe results.

Q6. NICE has ignored that many adults with PKU who have problems associated with high phenylalanine levels – like brain fog, depression or poor memory – simply cannot cope with dietary treatment. The NHS should not leave people without a realistic option for treatment. I also believes that NICE has undervalued the work and impact that managing PKU can have on adults with PKU and their families. The support work that goes into helping my son with diet is currently undertaken predominately by myself and my wife. Our aspirations for our son in the coming years is that he will go away to University. With this in mind, the use of Kuvan will be a very beneficial tool in my son living independently. He will have to prepare significantly less prescription foods as his intake of protein is significantly increased while taking Kuvan. This would materially help him to have a far more normal University land later life, while simultaneously controlling his Phe levels more consistently. Such benefits are not fully valued by the current NICE recommendations.

Q7. I can only offer anecdotal evidence gained due to being involved with PKU support groups. My observations are that there are substantial mental health issues associated with the lack of understanding associated with the condition. NICE do not place enough value on this effect and indeed there is a problem of a general endemic lack of knowledge of PKU as a condition throughout society. Thus authors of this appraisal are not empathetic enough to the traumas of living with a low protein diet.

Q8. I believe that the NICE report does not take account of the financial cost that helping to manage a PKU diet has on the family of a PKU patient. This is a relatively straight forward calculation, involving the number of extra hours involved in the preparation of a PKU diet vs a regular diet multiplied by the average UK wage expressed as hourly rate based on a 40 hour week. Although acknowledged by the committee in the ERG report I do not believe it has been empirically used within the QALY's calculation. Further there are many cases of loss of working hours for adults that can not adequately prepare a low protein diet and while also completing a full time job. This is not accounted for in the NICE review.

Q9. People with learning disabilities are at a higher risk of being unable to control their phenylalanine levels with dietary treatment. The need for help with dietary treatment might also restrict the independence of people with learning difficulties. NICE recognised that people with learning difficulties might struggle with dietary treatment but there is no evidence that this has been included in the cost analysis.

Q10. High Phe levels at such a critical point in neonatal development needs further studies and until these are done, NICE should look at a worse case scenario for the long terms effects of elevated Phe on the unborn baby.

Q11. *[no response given to this question]*

Q12. NICE has not considered the harm of Maternal PKU syndrome and the worry this can cause to women with PKU. When deciding that Kuvan is not cost effective in adults, NICE has ignored the benefits to women of using Kuvan to help women with PKU have safe and happy pregnancies. NICE has recognised that controlling Phe levels is important in early pregnancy, ideally before conception, and has recognised that this would reduce the risks of Maternal PKU syndrome. However the harms from high levels in early pregnancy have not been included in their cost analysis. I believe that NICE has failed to take account of the issues experienced by women with PKU and that this is a major failing in their draft guidance. Further at the point of conception there is a second life that NICE has not established any long term effects of a raised Phe level on.

Q13. The recommendations at the moment allow for Kuvan up to the age of 17 but not 18 and over. No studies have been done on the effects of a future 18 year old, moving from a relatively protein relaxed diet, to being restricted to a low protein diet of potentially less than half of that individual's previous daily allowance, due to the withdrawal of Kuvan. The recommendation, as currently written, are the cause of this problem and this will lead to all the problems associated with managing and coping with a low protein diet. NICE with their current recommendations are creating this problem. Kuvan should be a NICE recommendation for life.

Respondent 24

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Although our daughter managed her diet well, going away to university in 2001 at age 18 was a challenging experience, sorting out prescriptions, storage facilities and having to self cater. For a young person nowadays, permitting Kuvan only to 18 would be a tremendous disruption to their way of life at this age and cause difficulty and distress.

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. *[no response given to this question]*

Q6. *[no response given to this question]*

Q7. *[no response given to this question]*

Q8. *[no response given to this question]*

Q9. *[no response given to this question]*

Q10. Anything which effectively lowers Phe levels prior to conception and during pregnancy without a draconian diet regime being followed before conception should be actively explored. If Kuvan provides this it should be available.

Q11. *[no response given to this question]*

Q12. The cost for each individual child is likely to be high so it is a cost which should be taken into account.

Q13. Restrictions on the amount of Kuvan prescribed for all children seems prescriptive, surely those offering treatment should be allowed to prescribe the dosage which they believe is best for the individual under their care. The same would be true if Kuvan is offered to adults.

Regarding Kuvan for adults, if it enables the individual to say increase their allowance from 9 to 22 exchanges per day, this would increase their ability to function more effectively especially if work involves travel between sites/away for a few days

Respondent 25

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. This option is absurd!!! How can you expect to give this type of treatment until 18 years of age and then suddenly remove the privilege. PKU is a LIFELONG condition

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. N/A

Q5. The inability to function correctly if strict protein intake is not adhered to and is exceeded

Q6. N/A

Q7. Ongoing bowel issues which require regular medication, issues with teeth causing erosion from high acidic content of supplements

Q8. Family is a big part of an individual with PKU, the stress of “inventing” new foods which are not eaten, wanting to sneak forbidden foods, disagreements between family members

Q9. No individual should be penalised regardless of their additional problems

Q10. N/A

Q11. N/A

Q12. N/A

Q13. No comment other than KUVAN should be available to all and no restrictions made

Respondent 26

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. *[no response given to this question]*

Q6. *[no response given to this question]*

Q7. *[no response given to this question]*

Q8. *[no response given to this question]*

Q9. *[no response given to this question]*

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 27

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. You do NOT suddenly stop having PKU aged 18. The impact of increased phenylalynine levels just impairs your performance at Work or University rather than school.
One aspect of life that isn't considered is that the children of adult PKU sufferers are affected, irritability, lack of communication, depression, in a parent are all difficult to understand for a child. It will be confused for lack of love, indifference etc. Add to that the difficulty they find in planning for the future and you realize that the child is seriously affected.
These secondary considerations are completely absent from official discussions about PKU. I am not saying that PKU sufferers are not capable of raising children, I am saying that one reason they might need more support as adults is because of this extra responsibility.

Q3. I do not agree with NICE's view

Q4. I have no evidence that anyone has ever conducted any experiments into the long term effects. It is a rare disease but I have never been spoken to about my experience and neither has anyone I know with the disease. The support I have had has been very belittling in that most medical professionals have never heard of it (including GPs), and those that have do not consider it to be an illness worth their time.

Q5. inability to plan for the future. Brain fog means you can't see past the next 5 minutes. Procrastination. Anxiety. Forgetting people's names (even 10yr+ work colleagues). Inability to follow the diet -> instant gratification supersedes other considerations because, well, the future is not something I can even imagine.

Q6. PHE levels effects every aspect of your life, how you interact with work colleagues or friends, the food you eat, whether you drink alcohol or not, how other people see you and interact with you. I do not agree with this assessment at all.

Q7. impossible to evaluate. Significant all the same.

Q8. Yes they definitely should. It played a significant part of my divorce and the impact that had on my children was significant. PKU sufferers are parents so any negative behavioral impacts are significant to dependents.

Q9. I have no experience here

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 28

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. No. The treatment should be available to them after the age of 18

Q3. NICE's statements are contradictory

Q4. N/a

Q5. N/a

Q6. N/a

Q7. There will be additional costs which need to be explained however in the overall picture I would imagine these are minimal

Q8. Yes they should take into account the impact of PKU on other family members

Q9. No

Q10. More testing to be done

Q11. *[no response given to this question]*

Q12. They should provide the costs involved

Q13. N/a

Respondent 29

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. My son has pku and adhd, he is 19 years old, he has problems with his concentration, behaviour and able to work his exchanges out by himself. He has struggled with his diet all his life and has been warned several times about how much he weighs. He is 6ft but you can see his bones, he cant eat alot of foods that could help with his weight due to his pku. He goes to college but he does struggle with the work with concentration because of his pku. Going through his teens he would rather not eat at lunch time due to being different also as there is not much food he can eat he would always take his own food instead of being able to choose in the cafe. If he was given Kuvan in his teens it would have changed lots of things as he would have eaten more and during his lessons he would have been able to concentrate more as he wouldnt be hungry. He would have been able to eat more non pku food, if then at the age of 18 he was stripped of this freedom it would have been devastating for him. He had 7 exchanges going through school which could have gone up to 30 exchanges then imaging on your 18 birthday it got taken from him he wouldnt have been able to cope. It would be unethical. Would you take insulin from a diabetic just because they turned 18.

Q3. I do not agree with NICE's view

Q4. You cant say that the brain stops growing at the age of 18.
University of Rochester
Understanding the Teen Brain
It doesn’t matter how smart teens are or how well they scored on the SAT or ACT. Good judgment isn’t something they can excel in, at least not yet. The rational part of a teen’s brain isn’t fully developed and won’t be until age 25 or so. In fact, recent research has found that adult and teen brains work differently. Adults think with the prefrontal cortex, the brain’s rational part. This is the part of the brain that responds to situations with good judgment and an awareness of long-term consequences. Teens process information with the amygdala. This is the emotional part. In teen’s brains, the connections between the emotional part of the brain and the decisionmaking center are still developing—and not necessarily at the same rate. That’s why when teens experience overwhelming emotional input, they can’t explain later what they were thinking. They weren’t thinking as much as they were feeling.
So University of Rochester has proven that the brain doesnt stop growing until at least the age of 25.

Q5. My son has highs and lows but when he has his lows his mind is very foggy and he cant sort out his own exchanges and his diet, he struggles taking his own blood and still needs support to do this. When his levels are high above 600 his moods are not under control, he is very angry and sometimes can not control them.

Q6. Having high blood levels affects your past, present and future. If you go off the rails it will effect your future. If you cant concentrate in an exam that can effect your future. People are staying in education for longer if you cant concentrate while learning it will effect your present and future.

Q7. My son is effected by by low minerals and vitamins because of lack of certain foods, people have to pay more for fizzy drinks, since the sugar tax people with pku have to pay more for fizzy drinks, this is not a life chose if they want fizzy pop they have to pay more which is not nice. My son has anxiety will not approach people that he doesnt know and even people he does know he finds it hard.

Q8. I have lived with my son having pku for 19 years and from the word go it has been hard, firstly to understand what it is and how to deal with it, then having to keep on telling people what it is and explain it. I have spent so much time over the years cooking food, collecting food, ordering food, weighing food, reading lots of pku cook books, taking him to the doctors at the hospital, taking his blood all the time. There are a lot of hidden things that people dont think about. Then trying to get him to start taking it on himself. Cooking 2 different meals all the time, telling his younger brother that he cant eat his brother food.

Q9. It is unethical to take it away at the age of 18

Q10. N/A

Q11. N/A

Q12. N/A

Q13. Transition is defined as the movement from adolescence to adulthood in all areas, including home, health care, education, and community. Without support from Kuvan this transition becomes a lot harder than it needs to be.

Respondent 30

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. As a child/teenager my diet was mostly managed and supported by my mother. Once I was away from home and relied solely on myself for all my dietary needs, out in the real world with others, it was not sustainable to follow the PKU diet. Life as an 18 year old is difficult enough, finding my own way with diet restrictions was too much, I was not able to keep within my limitations.
When falling pregnant it was so hard to keep my levels where they needed to be, I was down to 2 exchanges of protein a day, while pregnant! This was totally unreasonable and ended up losing weight, and almost being put on a drip to help with my nutritional needs.
As a mother looking after a small child, my own dietary needs were the last thing on my mind. I was not able to continue breast feeding as I was not producing enough to satisfy my baby.
As an adult the impact of high levels of Phe is debilitating, confidence and mental health is low and affects me daily. My work has been impacted with illness caused by high blood Phe levels, my concentration levels are low and my ability and attendance is impacted by my mental health.
It is crucial to continue with Kuvan into adulthood as it can have such a detrimental impact on a PKU patients wellbeing, livelihood, career and enhance lives for the better.

Q3. I do not agree with NICE's view

Q4. *[no response given to this question]*

Q5. High Phe levels affects me in many ways. Physically I cannot maintain a good weight, I have skin complaints and allergies that can be very controlling. I get anxious and have very low self esteem when levels are high and this impacts my work and attendance, my social life and my family are also impacted by this. My moods are extremely temperamental which also impact family and work. The tiredness and lethargy that comes with high phe levels is life changing, it literally stops me doing anything, my energy, enthusiasm and motivation is non existent.
All of these things combined means I would not go outside for days at a time, I'd feel lonely around my own family and friends because I would be so introvert. The diet is isolating!

Q6. I do not agree. The amount of times I am at my GP's surgery because of the affects of high phe levels is ridiculous, from skin complaints to mental health issues that have affected me for as long as I can remember. I have seen dietary Psychiatrist for the issues I've had as an impact of high levels. I am concerned with the affect of my diet on my bones as I age too, I am already seeing some weaknesses that I can only imagine getting worse with age, as a result of my limited nutrition.

Q7. I have been medicated and treated for mental health issues for many, many years. The ongoing costs associated to this must be excessive.
I am always receiving treatment for skin complaints and allergies as a result of PKU.

Q8. Absolutely, as a child my mother was constantly having to care for me, until I left home.
As an adult the impact on my family is significant, the mental health issues obviously impact my son and my partner. The constant meal planning, and having to create different meals for me to the rest of the family affects all of us negatively, eating separately, different meals and at different times.

Q9. It doesn't sound like this has been considered fairly, everyone with PKU suffers high levels at some point. You only have to be unwell and your phe level increase.
Every person with PKU as a teen going into adulthood will struggle with diet and staying within their restricted diet limitations.

Q10. Consider the mother and the difficulties had to maintain such a low protein diet throughout pregnancy. The stress and anxiety that eating something could damage your baby is immense! the stress at this stage of your life is already high, adding the PKU issues makes mother feel completely out of control and helpless. The knowledge that you can cause damage to your baby by eating the wring thing is too much to

handle!
The lack of protein also makes the baby small.

Q11. *[no response given to this question]*

Q12. I think it is absolutely disgusting that this is not considered!
The impact the thought of this has on you as an expectant mother is phenomenal. Any expectant mother with PKU would give anything to reduce that anxiety and stress.

Q13. *[no response given to this question]*

Respondent 31

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. My son has pku and is 17 now. His life. My life has been so difficult sad demanding trying to follow a diet of pku. My son cannot see to his diet and is struggling to see to his own meals. Manage his exchanges as the diet is so restricted. Why can't he try kuvan. Pku is no different as a child to an adult. How dare you allow a child to experience some normality with eating and then take it away from them. How dare you. CRUEL very cruel and inhumane

Q3. I do not agree with NICE's view

Q4. My son is struggling with diet and taking suppliments. His hands shake and he is tired all the time and this is just the start or rebelling against the diet and regime

Q5. All of the above. Try living with pku then NICE would look upon it differently.

Q6. Doesn't any parent want the best for there child. Are we not constantly told on adverts By the government. By drs what to give your child from being born to develop into a healthy adult. Do NICE not understand the cost in future years pku adults might take on the nhs if not looked after properly

Q7. Not only is food and drink more expensive but what about time taken from work as a mother to look after our children's pku needs Baking. Appts supporting

Q8. Yes I do. I have two children one with pku and one without. My sons life is very hard and my life as a mother is too. Never relaxing always planning the next meal. Preparing. Ordering. Dealing with emotions. Dealing with the cruelty of not allowing my son a natural human need to eat our food. Always restricting him. It causes him anxiety and his family too

Q9. Everyone struggles with pku from any background. You try live with it every hour of every day

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. They need to actually speak to everyone with pku to get a fair result How can you offer a child some normality and then take it away

How can a child deserve a better chance of a quality life but an adult with the same problems not Who is making this decision. So you would treat a child who's diabetic but then stop when they reach 18. How can age matter. We are all human beings and deserve the same chance. Or are you saying the young only matter let's forget about the older generation

Respondent 32

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I think it is hard as a teenager coping with being different and eating different things from your friends and family. However this doesn't get any easier when you're older I am 32 and have PKU I feel I would benefit greatly from Kuvan or at least having the option. I had a baby and I would have benefitted from having it to help me control my diet if I wanted another baby I would appreciate having the option because its a lot of pressure and stress on the person who is having a baby. It's also a benefit when you go out for food because you can feel some sort of normality.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. Not necessarily brain damage but it still causes a lot of issues to the brain such as mood swings, depression, anxiety, memory loss and eating problems. This may not seem like a big deal to NICE but to myself it is and the fact it can be prevented or made easier would mean such a happier life. Not fearing your levels are too high or not remembering things.

Q5. It's horrible I can get anxiety from nowhere and not want to go out. I have anxiety from goigg out for a meal I always need to look at the menu before I go to make sure I can eat. Memory loss is awful I hate not remembering things as a result of high Phe levels. You can get depression as I've stated above and that is horrendous because you get the care free well I may as well eat what I want my levels are bad as it is.

Q6. It is necessary to take it into account because Pku uncontrolled still has an affect on brain functions. I appreciate cost is a major factor but Kuvan can give many families and adults with Pku a greater quality of life.
There is a lot from my past I don't remember and I struggled to control my diet when I was younger I get down from high blood levels and want to eat far more which affects my mental health further my anxiety and my weight. It all links up. I get my times with uncontrolled diet with depression and want to just forget I got pku but that makes it worse and its an endless cycle.

Q7. I suffer with depression, anxiety, weight issues and ibs from anxiety. Again a lot of these are from high Phe levels and not being able to eat things I enjoy.

Q8. Yes my mum when she found out was a mess she really struggled felt so guilty. My dad and mum had to make a lot of food for me and having to try and explain to me why I couldn't eat what they were eating. It's very difficult to explain to waiting staff because they just assume its a vegan diet or a life style choice. You feel very left out and put on show.

Q9. I appreciate it will cost a lot of money but we wod have a relatively normal life and be able to eat what we wanted within reason. No anxiety going out for food or struggling to decide what to eat for breakfast, lunch and tea this could be completely life changing just being given the chance would make a massive difference.

Q10. I think it should be used to help pregnant women because the stresses of controlling a diet like Pku while pregnant causes so much stress and anxiety. This is not good for the baby but also you as a mother with PKu have such high risks such as losing the baby, having a baby with a heart issue or beigg brain damaged without having PKU. That is scary and highly intimidating for a parent.

Q11. I had a baby and I struggled so much to control my diet usong kuvan would have taken a lot of pressure off myself as a mother. It's scary enough to think you could lose a baby but the fact that you could be the reason for that or your child could be born disabled from lack of control of your diet. It's hard with a little one when you have pku because you can't test foods for them because they're too high in protein and you don't want to risk having something you're unable to try that causes your levels to go high. Kuvan would be an extreme benefit I would like another child but having to have a well controlled diet after so long not having to worry is very frightening with the hell of kuvan it would be a relatively easier decision. I'd be able to feel more relaxed with my children eating high protein foods I can test for them make sure it's cooked or not too hot and not worry.

Q12. I think it should be considered because otherwise it could cost a lot more in health care and other services as a result which could be prevented with a simple tablet. You have many things to make people's lives easier such as inhalers for asthmatics I think kuvan would help PKU patients have such a better quality of life and be less likely to suffer with depression and anxiety.

Q13. Kuvan would be a life changing for so many children with PKu and adults and it should be considered for adults because it is so hard to eat the same thing and weigh everything everyday of your life and not enjoy what you eat or enjoy it but only able to have small portions.
For one exchange pku children and adults can have 45grams of chips why don't you weigh that out and see how that looks. Many children and adults can only have 5 exchanges which allows 5grams of protein a day you weight out 45grams of chips and that's one gone and it can barely fill a hole in hunger.
Please consider kuvan for adults as well because it will be such a huge impact on the lives of pku adults and children and give them a better quality of life.

Respondent 33

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. The PKU dietary regime is extremely complex. 85% of ALL food must be avoided because it contains too much protein, which is toxic to people with PKU and eating too much of it (even a few grams too much) can lead to irreversible brain and nerve damage. Meals must be prepared using prescription items - mainly pasta and flour - which are more difficult to cook with than 'normal' foods. It takes time and practice to learn to cook these foods to make a palatable meal. Measured 'exchanges' of foods containing normal protein must be accurately weighed and spread out evenly throughout the day. Protein substitutes must be taken 3-4 times a day and these are extremely unpleasant in taste and texture, and are very filling. It took me many years to learn to make palatable foods with limited ingredients, and the process of managing PKU, my daughter's refusal to comply with the diet and keeping her blood levels in the safe range was so time consuming and stressful that I had to give up full time work to ensure that she was kept safe and fed safely.
Research, lived experience and the NSPKU survey, Patient Voices: Listening to the Experience of People Living with PKU shows how people taking Kuvan can eat a more relaxed diet and also feel better in themselves. Now imagine those young people who have benefitted from feeling well in themselves and having a more relaxed diet. At 18, they are studying or have finished school and may be going on to further study or starting work. If Kuvan is taken away their phenylalanine levels rise and they start to feel the effects of this - mood swings, digestive issues, brain fog, low mood, difficulty concentrating (See NSPKU Research: Living with Phenylketonuria: Lessons from the PKU Community) and at the same time they need to learn how to cope with the restrictive PKU dietary regime - cooking PKU food, restricting what they eat, taking more unpleasant protein substitutes. They will be used to, for example, eating fast food with their friends and will no longer be able to do this.
I do not think that NICE has understood the reality and implications of living with PKU and the decision to give it to young people and then take it away is cruel and unethical.

Q3. NICE's statements are contradictory

Q4. Nice understands that people with PKU are at risk of brain damage. If brain development does not stop until age 25, why take Kuvan away at age 18? It does not make sense.
My daughter is 20, has PKU and is studying at HNC level. She has been diagnosed with specific learning difficulties and slow processing. She needs extra support and extra time because she cannot absorb or process the information she reads and suffers from brain fog. She suffers from anxiety which stops her from doing some of the things she wants to do, such as applying for a part-time job. She has a tremor which affects her ability to carry out the practical side of the course. She lives in fear that these problems will only get worse and will affect her career options and future. Her PKU consultant has referred her to neurology to assess the extent of the problem. These effects are common in people with PKU (see NSPKU research: Patient Voices)
Adults with PKU need the support of Kuvan too, not just children.

Q5. NICE understands that "children with PKU frequently experience difficulty with focus, depression or anxiety, disordered eating, digestive problems, headaches, low mood and sadness, feeling tired all the time and being in a heightened emotional state (including aggressiveness, psychosis and paranoia) because of high Phe levels." My daughter, aged 20, suffers from:
anxiety
tiredness
brain fog

poor short-term memory
digestive problems
NICE needs to understand that these difficulties are not limited to childhood. They continue into adulthood. Adults also need a treatment that can reduce PKU symptoms and give people with PKU and their carers peace of mind about blood phe levels. This is very important for adults who are trying to work and live their lives. 79% of adults with PKU fail to control their phenylalanine levels within prescribed guidelines and Kuvan would help them to do this. (NSPKU Research: Patient Voices: Listening to the experience of People Living with PKU)

Q6. My daughter has a tremor as a result of high levels. Metabolic consultant has referred her to neurology. It will not get better and is likely to get worse. She is training to be a makeup artist and will need a steady hand. Her PKU could seriously damage her prospects and future happiness if the tremor means she cannot work (or cannot work to the best of her ability) in her chosen field. People with PKU need Kuvan to protect their health and happiness for their whole lives.

Q7. NICE understands that there are costs involved with supporting people with PKU who are struggling with PKU and its effect on quality of life.
My daughter's struggle with PKU incurs/has incurred the following costs in addition to the basic costs incurred by having PKU and the additional costs incurred by the family:
DLA / PIP (higher rate)
Disabled Student Allowance - £3500 per year
Extra literacy support throughout school
Extra PKU consultations with metabolic team
Gastroenterology investigation
Neurology investigation
Additional GP appointments
Referral to Mental Health Team for anxiety
Prescriptions for four different laxatives
Consultations with clinical psychologist for behavioural issues

Q8. NICE understands that there is a burden on carers and families of children with PKU. This burden does not end at age 18. My 20 year-old daughter still lives at home because she has realised that she would not be able to cope with managing her PKU on her own. If she had Kuvan she would be able to relax her restricted diet, rely less on her parents and live more independently. Adults need Kuvan as much as children do.

NICE has not taken into account the impact of PKU on other family members when valuing treatments for PKU. I gave up full time work, changed career and experienced a drop in salary of 75% in order to manage my daughter's treatment and ensure her safety. This has affected our family's finances and my pension. All family plans, holidays and outings revolve around PKU and managing the dietary regime still takes around 20 hours a week. The stress and burden of managing the condition and observing her health and learning issues affects my mental health and my relationship with my other child and husband, because PKU and ensuring my daughter's safety must always come first.
NICE has not understood the full implications of having PKU in the family and has not understood that these burdens continue, unchanged after the age of 18.
See also NSPKU Research: Patient Voices: Listening to the experience of People Living with PKU, p.19.

Q9. NICE understands that some groups may have greater difficulty managing PKU through diet. NICE needs to understand that in those people who do manage their PKU within guidelines, the burden of doing so is enormous. It is complex and time-consuming. People give up work or work part-time in order to manage it and so are disadvantaged in financial terms and they cannot fulfil their potential .
NICE is not treating people fairly by giving Kuvan to some groups of people with PKU and not others.

Q10. The NICE committee is not aware of evidence to estimate the benefit to the unborn child of advanced phe control, but PKU is rare and this means that there may not be enough cases or studies to provide the body of evidence that NICE wants, however, it is a matter of fact that high phenylalanine levels are damaging to the foetus. See pages 16 and 17 of Patient Voices: Listening to the experience of People Living with PKU.
NICE must approve Kuvan to help women of child-bearing age to manage their reproductive health and mitigate the risks of maternal PKU.

Q11. My 20 year old daughter has already said that she is afraid to consider pregnancy and will probably not have children. She is afraid of the damage that her PKU will do to the unborn child and understands that it is very difficult to keep levels in the safe range for pregnancy, having spoken to women who have gone through this. She is anxious anyway and knows that the anxiety of pregnancy with PKU will be too much for her to bear.
NICE should approve Kuvan for women of child bearing age in order to help them achieve strict metabolic control and a normal, happy, safe pregnancy with a good outcome for the child.

Q12. Children of mothers with PKU born with neurological damage will, of course, cost the NHS and school system in terms of assessment and treatment, consultation s and school staff and interventions, not to mention the potential lost earnings of their parents and they themselves. It is a false economy to deny women Kuvan, which could be instrumental in preventing damage to the developing foetus. NICE should also consider the mental health, happiness and life experiences of mothers and children affected by PKU.

Q13. PKU is a condition for life and the 'diet' is for life. It makes no sense to treat only for 18 years and then stop treating. It is cruel and unfair.
NICE is not treating people with PKU equally by making this decision.
NICE has not given enough consideration to the realities and lived experience of those adults living with PKU.
Most other European countries - and many other countries around the world - understand the difficulty of living with PKU and prescribe Kuvan for children and adults, knowing that it will enhance their quality of life and allow them to be productive and contented citizens. It is very hard to understand why NICE does not value the quality of life of ALL people with PKU.

Respondent 34

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Wholly inadequate and unfair. At a time when many young people are pursuing higher education courses and embarking on living independently for the first time. By removing this life changing medication at such a crucial and precarious time of life you risk not only the current health but also the future health, wellbeing and independence of young people with PKU.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. It is well documented in the PKU community (please research this) that side affects are experienced in adulthood due high phenylalanine levels including memory issues, concentration and mood issues, not to mention more serious and concerning issues linked to motor neurone problems manifesting themselves as tremor, coordination etc

Q5. All of the above. Inability to concentrate, low mood and feelings of helplessness and inability to cope with day to day tasks. Feeling overwhelmed with the diet and balancing work, family life etc. Knowing this how can NICE justify withdrawing medication at 18. Nonsensical!

Q6. It is known that there are long term health issues linked to high levels. The extent is not fully known due to relatively new understanding and treatment of PKU. Uncontrolled levels may have resulted in poor education attainment and therefore the likelihood of lesser employment prospects.
In my own experience I have felt constrained by diet and unable to take certain jobs where I know preparing food in the workplace would be challenging. This included shift work which would have lead to promotion. Likewise I have felt unable to travel widely, as in the past carrying my daily medication and sufficient low protein foods abroad has been challenged. As a result I feel my life experience has been determined by my medical condition, which if that were a physical condition would be far more noticeable and unacceptable to others witnessing this. The fact that in many ways PKU is an unseen disability is unacceptable.

Q7. Additional costs will be incurred by the NHS in treating long term health arising as a result of uncontrolled levels. Some women with PKU have felt so overwhelmed with management of the PKU diet within the extremely strict limits required in pregnancy that they have been forced to give up the option of having a child. This will inevitably have long term psychological impact on them as it was not necessarily a choice but rather a necessity.
I was suitably supported medically and personally to manage a pregnancy successfully and without impact to my child. However that too has come at additional cost to the NHS through additional free dietary foods, additional Dietary and consultant supervision, additional antenatal appointments and supervision.
Within the PKU community I know of many individuals who experience anxiety and other psychological problems related to PKU and the additional pressure they feel in managing daily life and the complexities of diet.
The current approach by NICE is a reactive rather than preventative one and is entirely irresponsible.

Q8. Many parents of PKU children are unable to work or unable to work due to the time taken to look after all aspect of their PKU child's health. Food shopping and preparation takes a much greater amount of time due to the calculations needed to monitor protein intake of every meal, snack and drink. The planning that is required is not understood by those able to eat 'normally'. It is an unseen demand on family time. Furthermore, there is additional costs to purchasing PKU suitable foods. Whilst some are available on prescription in many areas this is restricted or unreliable. Therefore, supermarket alternatives are needed which are more than double the price and are higher in protein so not ideal. Whilst some families are able to claim benefits to support these additional costs the majority cannot, myself included.

Q9. I would say that every single person with PKU struggles with diet more than once in their life. Other than pregnancy I don't fall into any of these categories however at times I have really struggled to manage my diet, so much so that at times I have been off diet which is also very common. I would also argue that undoubtedly those groups may need help with diet but in my experience within my family and friends those individuals already are in receipt of help for those needs. Pku needs to be supported for all.

Q10. Kuvan should be made available to all adults in particular women of childbearing age.

Q11. I spent 2.5 years on preconception diet before becoming pregnant. Pregnant women and those planning pregnancy are required to lower levels considerably thank typically required for adults.The mental toll think takes is excruciating. Furthermore the impact on every aspect of my life was awful. I was unable to socialise normally with friends and family on many occasions as generally this involved eating in restaurants which rarely cater for PKU. I had to make special arrangements in work to prepare food for myself. All aspects of life were impacted despite my careful planning of my pregnancy and preparation of suitable meals. Overall this added even more stress and anxiety to the process of conceiving and carrying my daughter, a time which was made far more difficult by the constraints and risks of high levels .

Q12. Again NICE have fallen short in their appreciation of the longterm implications of uncontrolled PKU. As in the reminder of the population some PKU pregnancies are unplanned, for many reasons. Where pregnancy is unplanned there is additional risk of uncontrolled levels and impact to the unborn child. Those children will require some form of medical or social support likely for the entirety of their lives. Also through difficult pregnancies and not fault of the mother, including bad cases of morning sickness again the effects on the foetus can be extreme. Enabling women to more effectively manage levels in pregnancy will reduce the likelihood of their children needing medical attention and social care during their lives for issues relation in vitro complications.

Q13. I urge NICE to reconsider their stand point, as I see it their approach is short sighted best and discriminatory at worst.

Respondent 35

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. PKU is a lifelong condition my supplements are expensive more than i get on UC kuvan probly cheaper

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. Ask a competent Dr. why else would you spend "1200pm on supplements use your brain!!

Q5. Makes it awful

Q6. Pku turned me from an intelligent child to a dependent with well over 20 medical conditions

Q7. Definitely you should take them into account diabtetes is common drugs osteopirosis all caused directly or indirectly by PKU every single medical condition I have is

Q8. My family broken coz I was differeent

Q9. Autistic diabetes epilepsy COPD low income all my problems not taken into account, you not treated adults fairly and you provide kids with emla cream but not adults we were pricked with needles much worse than the ones you use today and many multiples as often

Q10. Your Dr, was an idiot then its well documented

Q11. get a proper doctor

Q12. you need a proper dr.

Q13. It should be used in adults read the european guidelines, typical tories cut costs in short term when long term costs get ignored and go through the roof like in my case for instance was a fnancial consultant had potential PKU destroyed it now over 20 medical conditions

Respondent 36

Q1. No, I think it should be available to everyone. My son is 24 and finds it very hard adhering to his diet. We've been waiting for this to be come available on the NHS since he was 14!

Q2. No

Q3. NICE's statements are contradictory;If adolescents and young adults are still at risk then it should be prescribed for everyone as if it's only 30% it will help it's a very small amount of children & adults.

Q4. No

Q5. As a mother I can tell when my sons levels are particularly high. He's tired, irritable, forgetful and moody and even his friends have commented on it. He finds it very difficult to stick to his diet but always finds he feels much better when he's gone back on diet,

Q6. Again as a mother I think it everyone should be given the chance to try Kuvan and if they are one of the lucky ones that it helps then it should be prescribed whatever the age. My son and other people over 18 shouldn't be discriminated against because of their age.

Q7. I think it is easier for an under 18 to comply with their diet as they aren't as independent. My son finds it hard when he's out or away with friends to stick to diet as it's not easy to take supplements etc with you which consequently means he's irritable, moody etc for a while until his levels start to fall.

Q8. Yes, it's a case of cooking 2 meals for dinner. We hardly ever go out as a family to a restaurant as there's very little on the menu. It's hard to see your child, teenager, young adult struggle with the fact that he thinks he's different from all of his friends. It's easier the younger they are but when they start getting more independent they want to be like their friends!

Q9. I don't think it's only the above groups that have trouble. I think generally males with PKU would have more trouble than females as I don't think as many males cook. Considering the small number that Kuvan can help no one should be discriminated against.

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. Considering there are only about 6800 people in the uk with pku and Kuvan will only help 30% thats about 2040 people. Surely everyone's quality of living should matter whatever their age. How can the over 18s be discriminated against, surely this is unethical. We're not allowed to discriminate against gender, colour or age so why can NICE use age to discriminate against the small number whose lives could be made a lot easier and enjoyable with the use of Kuvan

Respondent 37

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Whilst I appreciate NICE's decision and understand that there isn't just PKU patients to deal with in their role. It needs to be stated by people like myself living with Phenylketonuria that allowing Kuvan treatment until the age of 18 is NOT a good idea. The treatment does not stop once we turn 18, it is a life long battle to keep PHE levels under control, if not then a PKU patient has increased risk of further complications and even brain damage. It is not an easy condition to live with. In my experience, I struggled a lot during my teenage years, I am 21 now and still struggle but I can see how much of an impact not having Kuvan effected me. The other side to this, offering Kuvan to the age of 18 and then stopping said treatment is frankly wrong. The PKU patient must then take away a bearable way of managing PKU and manage the condition with crude forms of medication, manage a diet, deal with the ins and outs of living with PKU off Kuvan. It will not work, it will make a PKU patients life unbearable especially if they go from having a few Kuvan tablets a day and having a relaxed diet to having to take formulas multiple times a day, managing a very strict diet regimen in which one wrong ingestion could paralyze them with illness for the rest of the day, or damage them beyond our comprehension of understanding. Sometimes with PKU, the damage done is unseen, it is what the PKU patient is living with and sometimes that can not be expressed, I have been in that situation and still am. However, with the treatment of Kuvan that could change, taking the treatment away at age 18 is not going to work.

Q3. NICE's statements are contradictory

Q4. NICE said it themselves, that even young adults are at risk of long-term brain damage. Brain development does not cease until age 25, and even then the body still develops and as a human being we continue to grow and age. There is always the risk of brain damage due to the

nature of PKU. As PHE increases, so does the white matter on the brain which can cause irreversible damage. I have had plenty of moments in my life where it was clear to me my PHE was effecting me. Its not just brain damage, we have moments where we can not think coherently, can not speak properly or have trouble understanding other people and their emotions and the words they are speaking. Many PKU patients say this is like a "brain fog" and that it feels like you can not focus properly. In my experience it is all too familiar. Sometimes when you are younger you forget to take the medication or you eat too much of a food which increases PHE to a point it has a negative impact on your health. PHE management and how you feel on a specific day is very much fluid. One minute you can be fine and managing well, the next you are struggling to comprehend what is going on and you feel extremely fatigued and can not understand what is going on, only that you require immediate medication and intervention. It is a scary condition to live with at times. It is not as simple as "managing" it. The risk of brain damage or other health related complications are very real and are still present in later stages of life. It does not stop just because the brain finishes developing at age 25. Again, stopping the Kuvan treatment would increase the risk of medical emergencies such as these and if someone has been on Kuvan since they were a newborn and then have to deal without it and have a emergency I can imagine that will be very distressing and potentially lead to worse damage being done. So please, before making the decision to cut off Kuvan with an age limit, consider the effects and the detrimental impact this could have on someones life managing PKU.

Q5. Like I mentioned earlier. High PHE does effect you and can negatively effect your day to day life and how you live. My personal experience is I feel more anxious with high PHE and I can not concentrate, I had difficulty with my GCSE's because of this and it had a detrimental effect on my grades, even now in University it is very challenging and feels like you constantly hit a brick wall. The quality of life for any PKU patient in this situation is rather difficult and can become dire very quickly, It is a fluid condition and one that does not stop and requires constant monitoring. It is a life long condition and it can become very tiring and feels like there is no end in sight, it can leave you feeling depressed and inadequate, Kuvan could change that completely, there has been so many positive stories of Kuvan changing peoples lives for the better where they do not feel anxious and can live a (almost) stress free life. Many of us PKU patients have longed for a time where this can be possible and its frustrating knowing how close we are to that being a possibility but being told that possibility has an age limit? It works for no-one and leaves us feeling betrayed, Phenylketonuria is constant, it is exhausting, it is detrimental, we need the solution to be for everyone.

Q6. Certainly, high PHE effects everything atleast for me and in my experiences. I have noticed high PHE having detrimental impacts on my social life and even trying to manage voluntary roles i have undertaken. I just want to live a normal life, that can be hard when the high PHE strikes and you feel like your brain is in a bubble, there is a fog over everything you feel, say and do. You do not realise the potential damage you are doing to yourself and others. Sometimes, you just have to manage it. You shouldn't be expected to do that, but without possible fixes like Kuvan that is the life we live and it has a massive negative impact. Even with writing this, there is no real way of talking about how high PHE effects you without literally living with it. You just feel like there is a large anchor holding you down and you have to keep dragging it along. The cost effectiveness should not come into it, we are talking about people's lives here, and if Kuvan can help them lead a better life, a better life than I have had where it feels like even your own body and mind is against you, then that is worth it. Cost should not come into it, and that applies for ALL age ranges, not just under 18s.

Q7. Living with PKU is tough not just for myself, but also financially. I have lived with my parents all my life and while they have been amazing in looking after me, it has had serious financial effects. I have special food I eat as part of my and many other PKU patients diet, which costs money, we have to pay for the prescriptions and even with a year long certificate that can be very costly. There is also the medication, it takes up mass amounts of space. It is out-dated and hard to manage. Kuvan would potentially cut all that away, and it would feel amazing to only have to pick up a few boxes of tablets rather than entire crates of food and supplements to survive. I have lived with anxiety for a while now, if not caused by PKU, the condition certainly catalyses it, it makes it so much worse. I live with hand tremors too, a benign condition that I have found becomes more aggravated when PHE levels are high. Sometimes, it is hard to manage PHE, day to day PHE management is certainly not easy and even when managing it well, you still feel the "PHE cloud" overhead, draining you of energy and the will to keep going. It is extremely difficult and something I hope NICE begin to understand when they read such examples as this. Even then, the condition does not stop at anxiety and tremors, it keeps going with the brain fog, the fatigue, the social anxiety and doubts, the non-confrontational attitude that leaves you feeling weak and under-powered, no confidence or self-ability, the list is long and when you live with it every waking day, it is so hard not to give up. But as PKU patients, we try to keep going, we are so strong because of what we deal with, but deep down we are damaged by the lives we are forced to live by no fault of our own. The cost is high, both financially and more importantly, mentally.

Q8. NICE should take into account the experiences of those involved with looking after a PKU patient. My experiences have been painful and frustrating. From dealing with PIP where we was told to "get on with it" and "if he can put a potato and a vegetable into a pan, he is fine" to managing PKU in schools where ignorance is bliss. It frustrates me how everyone thinks it is just a diet, or something trivial. Growing up seeing my mother in particular upset and distressed at feeling ignored and as if you are banging your head against a brick wall is enough for anyone to feel a profound impact. When you deal with it personally, it just feels like a kick in the gut, it is exactly how this Kuvan decision feels. Parents should have a say within this consultation, they have brought up children dealing with PKU and it is so hard for them when they can not voice how they feel about matters like these. It effects them too, they worry how their child is managing at school whether the teachers are looking after them, whether they are eating or managing the diet and medication. I know in my youth i certainly wasn't thinking about it all the time because at that age you don't see what impact it could have on you if you do not manage it well. Even going on school trips was a nightmare, my mother usually having to come along to assure I was fed and medicated, that I did not eat anything I was not allowed. It is a minefield and extremely stressful for adults. It isn't enough for me to speak about it as a PKU patient, NICE need to hear it from the parents who dealt with it and often felt very alone as no other parent was dealing with it. Do not mute the voices of anyone in this situation, otherwise these decisions become even more unbearable to read.

Q9. I do not believe they have considered people fairly in this decision. My opinion is that every PKU patient deserves access to Kuvan, the trials that are done to assure we are responsive will cut the numbers down further, even when there isn't many PKU patients anyway. Cost effectiveness is in my opinion, inconsiderable when the number of patients with PKU is so low. Frankly, the medication and food, supplements, extra medication for deficiencies will certainly cost more altogether compared to funding Kuvan. I can't imagine its more expensive to fund Kuvan as a lone drug than everything we must have now to assure we can manage PHE levels and survive. Money should not come into it, we are a small community of patients, who have been waiting 12 years for this medication. While I understand there has been issues with Biomarin who happily made billions from medication, part of that being from Kuvan, we should not be waiting any longer and frankly, it is an insult to keep us waiting any longer. Please, let us work this out and allow access for all ages, not just a minority few when the pool of PKU patients is already small enough. Cost over life, no matter who or where the patient lives is not acceptable, especially after such a long wait.

Q10. Its been stated that women must control PHE before conception to assure the baby is born with no difficulties regarding PKU. I imagine its hard enough dealing with pregnancy itself, do NICE really expect women who are pregnant to deal with PKU on top of pregnancy? That is not acceptable by any means. It has already been stated that pregnant PKU patients require strict control of their diet and medication to assure the baby is as healthy as possible, again it comes down the fact only a small majority of the PKU population are going to become pregnant and have children, does NICE really want to cut them out? This should not be a debated decision, fund it for everyone and it wont be an issue, we have waited long enough as a community anyway, it should not be argued, give everyone the ability to live a normal life and have children as they wish without the added stress of PKU.

Q11. I explained it above in the previous point made, I can not speak of experience as I am not female but it should not be a debated decision. PKU patients should be able to create life, and be able to do so without the worry of PKU effecting any of it.

Q12. N/A

Q13. NICE, please consider everyone within this community, not just the few. Cutting Kuvan off as a child turns 18 and becomes an adult is not ideal and not acceptable in any form. It will not work that way and this decision needs revising. The evidence I and many others in the community have provided are explicit and real. Do not let us suffer any longer, ANY of us. It is frustrating we have had to wait so long, lets end this wait, end this unacceptable treatment of the PKU community. We must work together to come to this conclusion, that involves everyone within the community, no matter age, gender, pregnancy status or anything else that could possibly effect someone being given Kuvan. Think of those so desperately waiting for a solution , do the right thing. Thank you.

Respondent 38

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. *[no response given to this question]*

Q3. I do not agree with NICE's view

Q4. *[no response given to this question]*

Q5. *[no response given to this question]*

Q6. Disagree with NICE. When I was on a very relaxed diet as an adult, I experienced most of the symptoms mentioned earlier. In addition, I experienced problems with my eyes due to a build up of white matter at the front of my brain. This build up of white matter was linked to high Phe levels built up over time. I do worry about the long term effects of previously high Phe levels when I was a younger adult.

Q7. *[no response given to this question]*

Q8. Yes, NICE should consider this too. It is difficult for my wife and children to understand.

Q9. No.

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 39

Q1.I do not agree with stopping access to Kuvan at age 18.

Q2. I strongly disagree with the proposal to stop prescribing Kuvan at the age of 18. Medical authorities recommend that the strict PKU diet should be followed for life. In order to follow the diet successfully, strict dietary control is learnt over many years, and an 18 year old simply would not have gained the skills or knowledge to understand how to do this. PKU and its effects do not diminish at the age of 18 or at any age.

Q3. I do not agree with NICE's view

Q4. Our experience is that serious problems are caused by high phenylalanine levels such as reduced concentration, lack of energy and poor memory, as well as depression.

Q5. Brain fog’, forgetfulness, tiredness, confusion, low mood and feelings of irritability, and depression are all effects encountered from high Phe levels, which in turn greatly diminishes quality of life, career and relationships, and overall wellbeing

Q6. rain fog’, forgetfulness, tiredness, confusion, low mood and feelings of irritability, and depression are all effects encountered from high Phe levels, which in turn greatly diminishes quality of life, career and relationships, and overall wellbeing

Q7. As a family we have incurred costs for private treatment for psychological issues associated with PKU, and therapy for depression, and also received therapies through the NHS

Q8. Living with PKU affects all members of the family daily, has a great effect on family and social life, as well as more limited life choices

Q9. PKU affects everyone in the same way, in my experience, irrespective of other health issues, impairments, ethnicity or social background

Q10. I cant comment on this

Q11. I cant comment on this

Q12. I feel this is relevant and should be assessed, as any costs due to resultant damage would be borne by the NHS

Q13. Access to Kuvan would bring life enhancing help to both children and adults alike, and I believe when such a limiting condition is so easily treatable, there is a moral obligation to fund such treatments. People do not choose to have PKU and they deserve help to function more normally, as other people do. Funding Kuvan will inevitably in turn enable further research to newer and more effective treatments

Respondent 40

Q1. I strongly disagree with Sapropterin not being available to adults and also being stopped at age 18.

Q2. At the age of 18, the youngsters will likely still be in education, maybe at or going to University or into jobs. They will need to feel at their best and not suddenly have to start learning to follow a very strict low protein diet, including how to choose, order and take the protein supplements and try all the different low protein foods. Especially if they haven't had to be on the diet whilst on Sapropterin. This would be an awful thing to have to go through at a very important time in their lives - possibly the most important as they will be having to make choices on careers, degrees and the choices that affect the rest of their lives.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. As a teenager, when I was told I could come off diet at 17/18 years of age, and did, I developed a noticeable tremor in my hands. I would also behave irrationally and could be extremely emotional/angry/tearful. I believe now, looking back, that this was some kind of mental health problem, caused by very high phe levels.

Q5. When I have eaten something I shouldn't, or too much of something, I can tell due to how awful I feel the following day. I get headaches, feel irritable or angry and cannot concentrate - which isn't good at work. I get irrational anxiety and I can also get a 'so what' attitude and that can include my diet, so it can then become a vicious circle.

I work for the Police and work full time shifts. They are long shifts at 9 and 10hrs. Starting either 7am or 2/3pm, sometimes half nights if there are operations on or other policing needs.
I have to take 2 meals to work most days - breakfast and lunch or lunch and dinner. If I prepare and cook my low protein food every day, that could end up being ALL I do in between my shifts. Whereas my work friends will sometimes not bother to cook food and just buy from nearby shops or takeaways, I don't have that choice, if I want to feel well and perform to the best of my ability.
When we sit down to eat, I often get asked what I have and can sometimes, even now as an adult, get embarrassed if it's something that looks different. And as for the protein supplements, everyone always asks what I'm drinking and again, I get embarrassed, so I tend to drink them when I'm on my own - in the locker room or in a car if I'm on my own, to avoid the questions.

For our job, we need to keep fit and my work colleagues are all into their fitness in different ways. I am too, I love it. Unfortunately I don't get time most work days, to do much more than walk my dog. I try to run a couple-three times a week but it is often just once a week, and usually on my rest days. I also like to practise Yoga and do weight training, but again, on work days I just don't get chance. I feel at my best when I am able to train - to go for a run then do some Yoga practise or weights work, before a late shift, sets me up for a good shift at work. I feel calm and centred and ready for anything.

Therefore, if I were able to have a treatment that allowed me to eat more protein, enabling me to not have to spend ages preparing low protein foods, if I could just throw something in a bag for work - a tin of mackerel or tuna and a pack of rice or a potato to bake at work with some baked beans, I would have SO much more time for ME. To do the things that make me feel good.

With Sapropterin, my quality of life could be massively improved. In fact it would be life changing for me.

Q6. No, I do no t agree. Having high phe levels can affect your future health. I developed a tremor in my hands when I was off diet and it has never properly gone away. I also believe it can affect memory in the long term as my memory is not good at all. I also struggle with concentration some days and still suffer with anxiety, although not as crippling as it was when I was off diet, it has stayed with me until this day.

Q7. I am lucky in that I don't have any long term health issues, however I know that a lot of PKU sufferers have problems with both their teeth and digestive problems too, all due to the acidity of some of the protein supplements that we HAVE to have. This diet isn't choice, it is something we are born with that we cannot do anything about.

Q8. I think NICE should have taken into account family member accounts. My husband is also responding so he will have more to say on this. And I know my parents struggled with me when I was off diet, with mood swings and even bursts of anger.

Q9. I don't think NICE has taken everyone into account at all. I am one person who really struggles with maintaining my diet - I am in that 20% of adults who have difficulty maintaining my diet. It is time consuming, burdensome and I have been in tears over it at times, even recently.

Q10. That Sapropterin should be made available to women who need to start the pre-conception diet, which can be several months before they even try to conceive. It is extremely important that the phe is at the correct level before they consider trying due to the risks to baby of being mentally and/physically impaired.

Q11. This diet is one of the main reasons that I decided not to have children. The idea of trying to stick to such a challenging diet put me off and the thought of having a disabled child scared me. So I am childless.
My sister also has PKU and has two children. She really struggled in her second pregnancy, particulary, to keep her phe levels down. She had to eat so many calories to make sure she kept her phe levels around the right number, whilst also trying to stick to between 0-3g of protein a day, for the first few months!!? She also had to have extra protein supplements to also help with this. All this whilst holding down a full time job in the NHS, she was close to breaking point.

Q12. Not got any experience of this.

Q13. Regarding quality of life. Unless someone has lived with a diet that only allows the protein equivalent of a couple of slices of bread a day, or, maybe an egg (most PKU sufferers are on 6-10g a day), they would have no idea of the despair when it comes around to dinner time each evening and realising you have already had your quota - and more, of protein for the day and you will have to try and fill up on vegetables or salad, fruit etc., that are free of protein - or the rubbery low protein pasta, cardboard-like bread, that can sometimes be full of holes.
47 years I have been on this diet and, quite frankly, I am fed up of it.
Cost shouldn't come into it. We haven't done anything to 'get' PKU, we haven't drunk too much alcohol or eaten too much sugar/salt, it's not something that we had any say in. Treatments should be for the WHOLE of the PKU community.
To take treatment off people as they reach 18, which should be a time of celebration, is just cruel. To deny it to adults is ageist. It should be available for all of those who respond to it.

Respondent 41

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. This is ludicrous to let children get used to foods and quantities only for them to be taken away at 18 , also particularly in females what about pre pregnancy and antenatal control

Q3. I do not agree with NICE's view;Research studies have shown deterioration in adults who lapse diet after adolescence

Q4. Read NSPKU news and views , numerous examples of adult lives hampered by reduced dietary control resulting in inability to concentrate and very often loss of employment

Q5. All of the above

Q6. *[no response given to this question]*

Q7. Need for numerous prescriptions for foodstuffs and protein supplements, time off work to attend specialist hospital appointments which are in regional centres not local hospitals, with strict control of phenylalanine levels and compliance with diet ,supplements , regular blood analysis and hospital visits pku patients can keep well and avoid extended Health care costs , but this involves a life time of compliance

Q8. PKU is a whole family commitment from birth

Q9. Every person with pku would have learning disabilities ,sensory impairment and cognitive impairments if good control is not achieved ,this alters within a persons live , depending not only on extrinsic factors but also intrinsic ,if a previously well controlled adult becomes ill for example

Q10. Surely nice can recognise the importance of protecting future generations health and in doing so reduce future health care costs of what would be definitely brain damaged children if maternal control was not strictly adhered to for 6 months pre-nasally and
Throughout the antenatal period

Q11. The fear of causing irreversible damage to your unborn child is a horrendous responsibility

Q12. As above

Q13. People with pku have struggled throughout live with extremely limited diet and the consequences of poor control.The chance to live a more normal life with kuvan is immense and the psychological and physical benefits would be immeasurable. To allow children this is good but then to remove it at 18 is cruel

Respondent 42

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. If children have benefited from lower phe levels while having access to Kuvan, they will find it incredibly difficult to manage the diet if they can no longer have Kuvan at 18. This is also a vital transitional age where many children leave education to get jobs or leave home to attend university. The extra challenges that managing a stricter diet would bring could be too much for many people and cause huge amounts of stress and worry. If people were to subsequently have higher phe levels, their emotional and mental health could also be affected, even in the short term. I have PKU and am now 46. As a child, less was known about PKU and long term problems in adulthood, so my diet was relaxed before I was a teenager. I can vouch for the fact that once you have had a more relaxed diet, it is very hard to return to stricter rules, more supplements and low protein food. At university, I was inclined to 'cheat' sometimes to make life easier. As a teen, I developed a slight tremor and was often more tired than my peers. In my third year of university, I tried to keep my phe levels low, but as I did not enjoy any of the low protein foods which I had given up earlier in life, I started to lose weight and became slightly obsessed with this. I lost 21 pounds in 3 months but with help from friends and family, managed to turn myself around in time for my final exams. But, I can see that once your diet gets relaxed, it is very hard to go back again and this could likely be the experience of many PKU patients if they had to come off Kuvan at 18.

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. I try to keep my phe levels pretty stable so, even though they are a fraction above the recommended levels, I would say I only get mild symptoms of tiredness, low mood and anxiety sometimes. But, I am very aware that these would increase if I allowed my phe levels to spike too much.

Q6. I disagree. I know I was never an anxious child, so this has developed in adulthood, which may be down to slightly higher phe levels over time.

Q7. I had an incredibly difficult pregnancy due to having acute morning sickness alongside PKU. I was off work from week 6 and was unable to get out of bed until midday and then I struggled to keep down any food and all my supplements down(80 phlexy 10 tablets and 5 vitamins). I was on 2 exchanges for months, relying only on prescription foods which my body was not familiar with, to try to counteract the nausea and weight loss. I had a great dietitian at the time and was lucky to give birth to a healthy baby boy. But a few years later, I went through the first early

stages of pregnancy and sickness, only to miscarry at three months. This happened twice in two years, both times requiring operations under general anaesthetic.
Finally, because of the intense pressure of having PKU and not being able to cope with the diet, the sickness, the threat of poisoning my developing foetus with my high phe levels (induced by sickness) and trying to parent a small child, my husband and I decided not to keep trying. In trying to accept this and what I had been through, I suffered emotional problems, mainly anxiety and depression. The NHS has no doubt footed the bill for this. To this day, I still take a half dose of citalopram. If I had been of another generation and lucky enough to have been on Kuvan, I could have had more 'real' food to help with the sickness and would have had less supplements to keep down. It may have made the process less torturous and stressful, perhaps with a different outcome, without the long term sadness and mental health issues I have had to manage and the cost to the NHS.

Q8. As per my answer above, my husband had to support me through my pregnancies and try to work full time and care for our child. I strongly believe that without I could have managed the morning sickness better with a little more flexibility with the PKU . My husband also had to make the difficult decision not to have a second baby. He did not want to see me go through it anymore.

Q9. I think that people who face extra difficulties should definitely been given access to Kuvan if it can make a difference to their quality of life when they are already facing challenges. My experience of pregnancies as detailed previously is a personal example of this.

Q10. NICE should be recommending Kuvan as an aid to PKU women considering pregnancy, and they should all have opportunity to try this prior to conception. For those who are responsive, it could take off so much pressure, trying to maintain such low phe levels during pregnancy. It is well known that without very low phe levels in pregnancy, babies are exposed to phenylalanine in the womb which can cause both physical and mental damage.

Q11. I was 12 years old when my mum explained to me that I could never have an unplanned pregnancy due to high phe levels in my blood being capable of damaging my unborn foetus. I went on the pill at 17 and apart from my planned pregnancies, I have been on it ever since. I have had to change brands due to headaches, scares, discontinuations and other issues. I suffer with varicose veins and if it wasn't for PKU, I would have settled for a slightly less effective form of contraception.
Once ready for children, the pressure a PKU woman feels to keep her levels low both before and during pregnancy is phenomenal and can be very stressful. Add to this, the possible experience of morning sickness and a struggle to keep down the supplements, the baby is put at much higher risk and the experience for the woman is torturous. This was my experience 14 years ago and I can honestly say that every day is a trial, you worry and wait for the next phone call from the dietitian with your phe results. You do anything you can to save your energy, keep your phe levels down, and not be sick so you can keep down a bit more supplement. I physically could not get out of bed until midday for months, I was off work for almost my whole pregnancy and I couldn't leave the house for anything other than medical appointments until I was 6-7 months. Even once your phe levels are under control, you do not know for months, until the child is born, whether your prior sickness and high phe levels (however many weeks they lasted for) has damaged your unborn baby. That is very hard to live through. Please see my previous answers for more on my experience of pregnancy and miscarriage with PKU.

Q12. They should factor this in and it would be costly.

Q13. There are many valid reasons why Kuvan should not only be considered for children up to the age of 18. PKU in adulthood can be very challenging and if not managed correctly, high phe levels can lead to a variety of long term mental, physical and emotional health problems, causing distress to individuals, families and financial cost to the NHS. The benefits of Kuvan for maternal PKU patients could be very positive and should be a priority. Patients with PKU have this condition for life. We already suffer with a condition that most people do not understand or have heard of, we already do not have free prescriptions and it is time for PKU to be recognised as the challenging condition it can often be. Kuvan is a way to help some PKU patients improve their quality of life. It should be available to them for life.

Respondent 43

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I am 33 and have grown up with PKU. I took part in the clinical study for Kuvan around my late teens/ early 20s and am still taking kuvan on a daily basis. First of all I have both felt the effects of kuvan and seen them in my blood tests so I can confirm it does make a considerable difference. With this in mind to allow someone access to it until the age of 18 and then take it away will have a big impact on their lives. They will suddenly have to become far more strict in their diet and far more dependant on support and supplements at a time in life when they should be starting to become more independent.
If the point is made that they can choose to come off diet at 18 and so it wont make a difference, it has been confirmed by NICE themselves brain development continues to 25. So by stopping at 18 they are knowingly exposing patients to the risk of brain damage should they stop the medication but continue with the same diet. Meaning patients would have to go back to a far stricter diet in order to avoid these effects.
Having something taken away from you is far tougher than never having had it in the first place and so by doing this I believe there would be an upward trend in people who have had their kuvan supply stopped continuing their existing dietary habits and so exposing themselves to the risk of long term brain damage.

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. High Phe levels do cause a 'brain fog' effect at any age. I have been off diet both with and without the kuvan pills and I have noticed a considerable difference when taking the medication. The symptoms listed above are accurate and were increased when I did not have the pills. Irritability, forgetfulness and difficulty focusing were particular effects I noticed and still do today but at a much reduced level.
The severity of these effects is directly linked to the kuvan and even if I were to miss a week of the medication I would see them increase almost instantly. Therefore removing kuvan access at any age will definitely impact on those who suffer from PKU

Q6. *[no response given to this question]*

Q7. *[no response given to this question]*

Q8. PKU has a massive impact on everyone connected to the individual diagnosed.
Immediate family are impacted as a child with PKU requires more care than one without. Their food must be measured. Some must be home made from scratch. Tools are bought to help this such as bread makers, plastic cups, flasks, separate shelves and containers needed to keep food protected. Then you have the time sacrifices, educating themselves on the diet, the time to make and prepare all the low protein meals and foods, making formulas and supplements, blood tests, doctors visits. Then you have the same issues when the child is outside of the home, having to chat to friend's parents to educate them of the risks of feeding the wrong food and drinks. Buying low protein versions or non sweetened items for them especially. If travelling do you have the necessary resources, a cooler, space for all foods and items. How long can you travel for before you run out or the supplements/ low protein foods expire.
There is a vast impact on those around the patient as well as to them individually both financial and time. My mother had to quit her career in order to provide the level of care I needed. Not only showing the amount of time and effort it requires to care for a child with PKU but also the financial impact as the household income was drastically impacted.

Q9. All answers I have given so far are from the point of view of a person for whom PKU is their only known long term health issue. From this point of view I believe Kuvan should be made available throughout adulthood. However, for those listed above these difficulties are magnified greatly. Trying to explain to a child with autism why they cannot eat certain foods or limited amounts of certain foods. A person who can only communicate through sign language explaining to a restaurant why they cannot have certain ingredients and need their order altered in some way. Those who do not have regular access to a pharmacy or GP for support on prescriptions and low protein supplements. Not to mention the added time and cost tot he families and friends who support these people. These are just a few examples of the impact this diet could have.
I believe NICE needs to very carefully consider the impact not having access to kuvan would have on these people and the massive increase to quality of life it would provide, not just to the patients but their families and support networks as well.

Q10. A person with PKU will tend to see their intake of protein increase, though very gradually, as they grow up. So a person who can handle 2-3 grams of protein as an infant will perhaps be able to handle 7-8 when they are teenagers. This obviously helps maintain a healthy diet as the body will require more nutrition as it grows and develops. When a woman with PKU becomes pregnant, she is then only able to take in the level of protein the baby can handle...not herself. Essentially she has to reset her protein tolerance back to when she was a child. Now an adult consuming a child's levels of protein is clearly not ideal but when that adult is also carrying a child this becomes a huge struggle. Pregnant women with PKU need to support themselves and their child's health whilst on a fraction of the protein a normal person WITH PKU would have, never mind a fully healthy mother.
Access to kuvan would enable the mother to have a closer to 'normal' diet and so benefit both herself and her baby through pregnancy.

Q11. *[no response given to this question]*

Q12. If a woman with PKU goes untreated during pregnancy research shows that child can be severely affected from birth. This will incur further costs in the long term. That child will need support for learning disabilities, dietary support, social care, special education. All costs that could be avoided if the mother had received the correct support and care during pregnancy

Q13. As a patient with PKU I believe Kuvan should be made available for ALL who live with this condition. I took part in the clinical trials and still take the kuvan today and I can confirm IT DOES MAKE A DIFFERENCE! It has improved my quality of life as it reduces the 'fog' that can heighten things such as; irritability, inability to focus, forgetfulness and a low mood to name a few. This is from a 33 year old who has no other major health conditions. For those who are in one of the categories previously mentioned where they have another health condition, are pregnant or are below the age of 25 this will have even more health benefits both short term and long term and for not only themselves but for the support networks around them. To reduce these categories to just those under 18 puts the health of all others at SERIOUS RISK. If NICE is truly concerned with protecting the long term health of all who live with PKU then the MINIMUM category to consider is ALL under 25 and those with other serious health conditions. Though access to this drug would drastically improve the quality of life of anyone with PKU of any age.

Respondent 44

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. It is immoral and wrong to give Kuvan to children and then take it away age 18. Having this drug changes people for the better. I have spoken to people with PKU who have taken or are taking Kuvan and it improves their dietary choices AND their wellbeing and mental health. It would be cruel to withdraw this drug from them when they reach 18, and would have to learn to live on a very restricted diet and start to experience the side effects, such as tremors, tiredness, digestive issues, feelings of isolation and low mood that I suffer. I am 21 years old and manage my diet very well, but this is because I still live at home and have the full support of my parents. I would not manage the diet and all the administration and organizing that goes with it if I did not have support. 18 year olds who have to come off Kuvan would be in a difficult position and would not cope.

Q3. NICE's statements are contradictory

Q4. I am 21 years old I have a tremor. This could affect my life chances and career choice to become a makeup artist. My consultant has confirmed that it is caused by PKU, despite controlling my levels well. My brain is damaged and I am not yet 25. (Also, the brain continues developing for life.)
Why would you even consider taking Kuvan away at age 18, knowing that the brain is still developing? It is cruel and immoral. Taking Kuvan away is purely for financial reasons, not for the best interest of the patient. This is immoral.

Q5. I suffer from tiredness, brain fog and a tremor. I have been diagnosed with dyslexia and slow processing. This makes it hard for me to follow instructions about my PKU diet and everything takes longer for me to do. Having PKU involves a lot of reading, understanding and working out.

Q6. High phe levels in childhood - for only a short time - have left me with a tremor. This is very likely to affect my career goals and life experiences. I am training to be a makeup artist and need to have a very steady hand. If I cannot follow my dream, my ability to earn a living is affected as are my life chances and my mental health. I would not be able to contribute to the economy if I cannot work, or have to take unskilled work.
NICE needs to understand that money spent on Kuvan will be saved in other areas such as mental health provision healthcare provision and benefits.
Nice must take into account quality of life and moneys saved in other areas when calculating cost effectiveness.

Q7. I suffer from bowel issues for which I have been referred to gastroenterology at the hospital.
I suffer from a tremor for which I have been referred to neurology at the hospital.
I suffer from anxiety for which I have been referred to the mental health team.
GP appointments to discuss the above.
Prescriptions for four laxatives.
I have had extra consultations with my consultant and dietitian to try and resolve PKU related concerns.
I have been awarded PIP at the enhanced rate.
I have been awarded Disabled Student Allowance.
Throughout school, I needed extra support and interventions in maths and literacy.
When younger, I was referred to a clinical psychologist for behaviour problems.
This is in addition to the extra costs of having PKU which are borne by my family, such as buying and cooking different foods, paying a maths tutor, my mother's vastly reduced income.
PKU prescription foods and protein substitutes.
Money is waited on PKU prescription items which are very often incorrect.

Q8. The whole extended family is affected by my PKU.
Mum's income reduced by 75% so that she could spend more time caring for me and ensuring my safety.
Travel and holiday plans are affected.
We have to have self-catering holidays, so Mum never gets a break.
My grandparents have learnt about PKU and have to store and cook PKU foods when we visit.
We are limited to only one local restaurant when eating out - and it's expensive.
My parents spend over 20 hours a week managing my PKU and cooking separately for me.
My mum's mental health has suffered. It is a great source of anxiety and stress for her.

Q9. NICE has not properly considered treating people fairly. It is not fair that some groups are awarded Kuvan and some are not. PKU is a lifelong condition which worsens with age. The PKU diet is a diet for life, so treatments should also be for life and for all sufferers.

Q10. It is indefensible that NICE would not allow young women access to Kuvan, knowing the risks to the unborn child of an unplanned pregnancy, or the anxiety caused by trying to keep levels safe in a planned pregnancy in order to avoid damaging the unborn child.

Q11. I am 21 years old and the thought of having to get my levels to a lower, safe range before even starting trying to get pregnant, then keeping them there whilst trying to get pregnant and keeping them there for the whole pregnancy, throughout morning sickness, etc, is horrifying and I am already dreading it. I am terrified that I will not be able to control my levels and will damage my unborn child. I am so afraid that I will probably not have children. This makes me very sad.
This affects my relationship with my boyfriend.

Q12. It is well known that the children of women with PKU can be damaged by high phe in pregnancy. It is indefensible that NICE would not approve a drug which could help to prevent that damage.
Children with neurological damage cost the NHS in terms of diagnosis, assessment, treatment, therapy, benefits and care. Not to mention distress and support for their parents and family.

Q13. NICE has not listened to the lived experience of people with PKU, or to the experiences of those who are currently benefitting from Kuvan.
It is immoral and cruel to approve a drug and then take it away at age 18, especially given the known difficulties of staying on the PKU diet after being off diet - listen to the lived experience of people who have tried to do this, such as Paul McKellar.
It is unfair to approve Kuvan for one group of sufferers and not all. PKU is for life.
Kuvan might be expensive but there will be savings made in other areas, including allowing people with PKU to be much more productive, healthy and happier people.

Respondent 45

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. This is a really bad idea. The discipline you need to manage the diet needs to be formed at a young age. The expect someone to be able to eat freely and then start on a strict diet is unmanageable. Once you have a taste for certain foods you don't want to give them up. The reason I manage my diet so well is because my Mum was so careful with the diet and didn't give me foods like yogurt, chocolate and used my exchanges for real food that would fill me up like vegetables and potatoes.

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. The psychological effect as well in knowing you've eaten too much protein and this can be dangerous.

Q6. Of course it's necessary to take into account the long term effects of high and ow PHE. These effects will have a detrimental effect on peoples lives in the future and the amount of care they will need.

Q7. I managed the diet well and am lucky i don't have health issues.

Q8. PKU effects families and friends of people with PKU in many ways. For instance where you can stay on holiday. It's necessary for people with PKU to be able to cook their own foods as restaurants can be limiting. Choosing restaurants where everyone can eat, it's much harder for people with PKU. If children need time and encouragement to take their PKU drinks. My Mum gave up work to look after me as she couldn't trust someone else to look after me. Children's will always ask for things they shouldn't eat or can only eat limited amounts of, a carer could easily give in but parents have know the long term issues and are more likely to stay firm. I had to take my own food to every party I went to and at my own birthday parties while all my friends ate normal food I had very unappetising looking PKU food.

Q9. I don't feel NICE is being fair in their evaluations. As mentioned in my previous answer tit takes a lot of time and effort to look after a PKU child. Those people on lower incomes and with lower intelligence levels will find it much harder to care for someone with PKU. These people should absolutely be offered Kuvan.

Q10. Managing PHE levels at any time is hard work and challenging. Pregnant women have to be very careful and manage a controlled diet that changes throughout the pregnancy. Kuvan can help manage these changes so should of course be offered.

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. If you've never had PKU you can't imagine how life without eating 90% of the food around you. How restrictive eating is and how hard it can be to find food you can eat outside of your home. You can't images what it's like to have never eaten chocolate or bread. i challenge the team at NICE to live 2 weeks on the diet of someone with PKU and then consider how life changing this treatment really is for people with PKU.

Respondent 46

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. This is a very bad idea. What happens when young people reach 18 years and are suddenly cut-off? They will quickly have to learn to restrict their protein intake more drastically than they have done in years, or ever. This will happen while they are finishing school or college, doing exams, going off to university or to live in their own place, etc. And at a time when they are likely to be starting to try alcohol. It seems extremely likely that their phenylalanine levels will go through the roof at that point. Not to mention those over 18 are people and they deserve the only oral medicine for their condition too.

Q3. NICE's statements are contradictory

Q4. It is well known that adults with phenylketonuria have abnormalities on neuroimaging, e.g. PET and MRI. The clinical significance of these is unclear. It is possible that they relate to mild cognitive impairments, executive function difficulties, or poor mental health. To say that “there is no risk of long term brain damage” is therefore premature, and further research is indicated. It is also inconsistent with the current guidance to stay on diet for life.

Q5. I suffer from severe tiredness, chronic anxiety and low mood, slow thinking. This definitely makes life extremely hard and unpleasant at times. Whilst I cannot attribute the entirety of these problems to Phe, it is likely that phenylketonuria and poor control contribute to or exacerbate these symptoms.

Q6. The cost effectiveness calculations are completely invalid if one does not account for all the possible benefits of treatment and all the risks of denying treatment. Inadequate treatment of phenylketonuria will almost certainly cost the NHS through additional appointments, treatments for cognitive impairments, treatments for mental health difficulties etc. Also, the prognosis for elderly people with poorly-controlled PKU is not yet known; there could be significant care needs later in life of poor dietary control is combined with neurodegenerative disease.

Q7. Undoubtedly, there are associated health issues. NICE has been extremely shortsighted to omit these. In my case, and that of a sibling, our phenylketonuria is associated with mental health difficulties.

Q8. Yes, but I don’t have a relevant experience to share. I have no doubt that being a parent of a child with PKU must be incredibly stressful. Stress leads to illness, that is pretty well established.

Q9. It doesn’t sound like these have been adequately examined. All of these groups can reasonably expect to be offered the only oral medication available for this condition. There is a moral obligation to assist these groups.

Q10. Sapropterin should be made available to pregnant women. The level of dietary control required of them massively impacts their quality of life. I would have thought the massively reduced risk of disability that results of enhanced Phe control would count as a benefit to the unborn child?!

Q11. I don’t have specific experience but please note my comments above.

Q12. This is an unjustifiable omission. The costs of long term care for children born with neurological damage can be very substantial. Not to mention there is an ethical imperative to prevent this outcome.

Q13. Based on the above it seems that the assessment was insufficient in scope and therefore extremely flawed. It is clear that the authors of the report have little understanding of what it is like to live your entire life on an extremely restrictive diet, to live with constant guilt and worry regarding your dietary control, and to have to deal with associated co-morbidities.

Respondent 47

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. As a teenager I think that learning to control my Phe levels caused me to grow up a lot quicker as I was responsibly for looking after my levels when I was on school trips, traveling, staying at friends houses, on nights out.

I don't think that the use of KUVAN should stop at all after the age of 18 (assuming that it is still effectively). This would provide many, many other people with the opportunity to eat and drink more of the things that they want.

I believe that it would be very hard for adults to only then start taking major responsibility for their Phe levels once turning 18 without the education and support that they could get already growing up with PKU through the NHS. I think that you could therefore potentially find that their are numerous more adults who can't keep their Phe levels under control.

As a result there might be more people getting forms of brain damage etc. at a later age - which some might consider makes KUVAN null in void.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. I have heard many stories about people with PKU suffer from forms of brain damage in adulthood. In fact when I was talking to my consultant who was trying to recommend going off diet about job prospects if I went off diet, he was talking about plastering or other practical jobs which I am not in the slightest.

I am studying languages at university and therefore have to consistently have my diet under control so that I can learn and retain language knowledge successfully. I would hope that Kuvan would be considered for people over the age of 18 so that I continue to learn and speak my languages. Kuvan would make my life a lot easier and means that I could work/ live abroad in the future.

Q5. If ever my Phe levels were high, I would experience all of the symptoms from above and I am 20 years old. As I said before, I am studying languages at university and hope for a career to do with languages in the future.

Q6. "it is not necessary to take into account the long term effects of high or low phe levels in adults" - I think that is ridiculous! life doesn't stop after the age of 18 years of age - there is plenty of time to cause irreversible brain damage.

Q7. I haven't found that I have been depressed etc. from PKU because of the good environment that I have surrounded myself with (friends and family). I have noticed that I can get too angry at the smallest things which the normal person wouldn't normally do.

This is something however that NICE should have looked into because I know that there will probably be a number who aren't in a similar situation to me.

Q8. KUVAN should be considered for all. Every time I leave the house I have to think about whether or not I have taken my supplements (Cooler 20's) or if I should take them with me. My family feel as if they constantly have to check on me to ask if I have remembered to take my supplements.

Additionally I have to consider the supplements when I go through airport security. As a family we have to limit ourselves to a few restaurants when we go out because they are accommodating to my PKU diet and the low protein foods that I have to use in exchange.

My family and I feel as if we are constantly being stared at every time I have to take out a pizza base in a restaurant to ask if they could put the topping on even though it is for a good reason.

Q9. All this is telling me is that NICE have picked some different groups of people for the sake of showing that they have tried - because it's all "due to the cost effectiveness estimates in adults".

Because you are an adult doesn't mean that you are necessarily allowed more exchanges of protein over a child. Some adults are on next to no exchanges of protein and unsurprisingly struggle with keeping there levels under control and aren't going to get support from NICE. unfair - suggests that they have just given up on the already existing adults.

Q10. As a young man with no kids myself, I don't know what I would be able to properly comment on this, however I do believe that a mother with better control of their Phe levels would help give birth to a healthier child.

Q11. Yes! I think that this is something that should be considered from child bearing age. We know that contraception isn't always reliable or used. This should particularly become an idea to be considered when the suffers of PKU start university.

Q12. Probably because like they have said before - it is hard to model but I would hope to know as much information as possible.

Q13. NO.

Respondent 48

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. In my opinion it doesn't really seem fair. To give a child all these opportunities with their diet and then take them away. I understand that there are more options these days in terms of low protein foods but realistically 'normal' food always will taste nicer. So for a child growing up to have these 'normal' food options taken away just seems harsh. One of the reasons I have been able to adhere to a strict diet is because my whole life I have the same diet. If I had eaten a certain way my whole life and then these food 'privileges' were taken away I believe I would find it much harder to stick to a new diet, one which is far from convenient.

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. *[no response given to this question]*

Q6. The statement by NICE is honestly shocking, I understand the focus on calculating cost effectiveness but I don't think NICE understand how much of an impact high Phe levels can have. Currently I am a university student, in university it is of paramount importance that I maintain low levels so that for exams and lectures I actually give it my 100%.

Suppose I did have high Phe levels for one week before exams, (generally for me if my Phe levels do go on the higher I tend to get frustrated quickly, my brain feels foggy and I tend to be irritable) the entire week I need to be focused on revising I may struggle so much more. Then, if I do not attain the grades I require this can obviously greatly impact my life and my future. There are countless other examples I can give but my main point is that no person should have to live and in a state of brain fog, tiredness or even depression since NICE decides it needs to cut

costs.

It's ridiculous to consider cost cutting if the cut directly impacts someone's life in such a major way.

Q7. *[no response given to this question]*

Q8. *[no response given to this question]*

Q9. I have classic PKU and currently have 15 exchanges of protein a day. I rely greatly on my low-protein prescribed food items. Over the past 2 years at University I've had many problems with my pharmacy sorting these foods. Since PKU is a rare condition they simply do not understand how essential it is for me to get items like low protein pasta, bread or flour. This is not just something I can buy in a shop. Sometimes I've had to wait upwards of a month from the date I have ordered my food. This has resulted in me borderline starving myself and eating a diet consisting of what little low-protein food I had left at home, vegetables, and the most calorie to protein efficient meals I could think of, mainly just bowls of rice with butter.
Normally I would just be able to go to the shops buy whatever food I desire for the week, cook that food and have no extra hassle or stress. Due to problems just obtaining food I've had to unwillingly change my portion sizes, what I want to eat and have no option to be creative with what I make. If I was less strict with my diet I may have been tempted to eat non-low protein foods, rather than starve myself, which would have increased my PHe levels and even further affected my mental and physical health. Clearly I have had more problems manging diet than a regular person, so no I do not think NICE has considered treating people fairly.

Finally this one example is just a recent one, I've given is one from a countless list spanning all throughout my childhood. My life is manageable since I am used to it, but this doesn't mean it's anywhere near as easy as someone on a regular diet.

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 49

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. This proposal is ridiculous, I spent the first 18 years of my life on diet, managed and controlled fantastically by my parents. I was taught how to manage the diet and how to cook with the diets low protein products (which in itself is a challenge) through my teenage years and before. I am now 44 and find it impossible to manage the diet properly whilst struggling with classic PKU symptoms of depression, anxiety and fatigue through high protein levels and getting stuck in the never ending cycle of being too fatigued to cook from scratch for every single meal regardless of how I'm feeling feel. Also at 18 years old I was having 5g more protein a day than I am now because as an adult you need less protein. Which could see future young adults loosing a much bigger percentage of their availble protein each day. In my opinion as an adult PKUer it is harder as you have no to manage it for you and more responsibilities.

Q3. I do not agree with NICE's view

Q4. My mental health has been in decline for sometime now. I have had to recently give up work because it has got that bad that I can't manage my diet, work, pay my bills on time, bring up my daughter and care for my partner. I have worked for 30 years, never been out of work but I'm in huge debt and my dietary management has been the other thing that has suffered massively.

Q5. I struggle daily with all of the above. For me one of the worst things after tiredness is the inconsistant moods one day I'm feeling like a warrior and can take on anything. Then several weeks or even months later I feel like I'm drowning and up to my neck in it and just can't cope. I end up wanting to hide from the world. Lost count of the times I have taken on a new job or got my self on a course for example, which I am more than capable of doing but its extremely frustrating hitting a point where I undo everything I have worked for. I know I am not achieving what I am very much capable of doing. Then when i'm out of the downward cycle, I'm feeling invincible again and so the cycle begins again.

Q6. Yes, the same as the above answers

Q7. I'm unfit to work currently so I'm having to claim benefits. The prescritpion products I have are already extremely expensive and I wouldn't so many of those presumably.

Q8. Yes. Lots of stress and strain added to families especially the mood swings and irritability, the lack of energy definitley affects quality time with children too.

Q9. Everybodies situation is different and some peoples challenges are worse than others, but everyone who faces challenges struggles with them and all deserve to have they're lives improved regardeless of whether its deemed as worth while as another persons. Anything that helps albeit a lot or a little it can be life changing for their personal battle. We have already waited 12 years with the hope of getting some improvement to our lives.

Q10. Everyone should get a chance to improve their lives with the best options for managing PKU regardless of cost versus benefits.

Q11. N/A

Q12. N/A

Q13. Personally I think a huge amount of focus has been put on children with PKU which I understand fully. However, it seems to be that there is a massive lack of knowledge/understanding on how PKU affects adults. We need very much to get past this stigma that adult PKUers aren't

really affected. I personally am fed up with being told that the diet works when in your own figures you state that 30% of adult PKUers have stopped diet and 20% have difficulties maintaining it. I don't think a 50% success rate for the diet shows that the diet is working. I would be interested to see figures of how many of the 50% of adult PKUers who are on the protein restricted diet are 1) managing it completely by themselves, 2) Have it managed completely by carers and 3) Have some help managing it.

Respondent 50

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I am an adult with pku who currently takes Kuvan, but at 18 was on a controlled and supplemented diet.

For me this was an important time in my education and life.

I moved away from home to university, putting me in complete control, (and meaning full responsibility for) my diet for the first time.

Hand in hand with this also came many new temptations and pressures, meaning that following a strict diet became very difficult, as I did not have my trusted support network around me. Indeed it was only in the years after returning home from university that I was able to get back to a proper, supplemented pku diet.

To grow up with the freedom Kuvan gives and then to have that taken away, at a time perhaps of great personal change and challenge would be very difficult.

There can never be a good time to remove access to Kuvan, but it strikes me that to take it away at this time in life, when people are perhaps just starting to make their own way in the world, maybe away from home, starting work or further education or both is cruel and torturous.

Q3. I do not agree with NICE's view

Q4. *[no response given to this question]*

Q5. I recognise all the symptoms and the worse they are the less you care, therefore the less likely you are to do anything about them. The irritability also makes life difficult for those around you, even those trying to help.

Q6. I only have quite mild pku, but I know that even in adulthood when I have ignored my diet, for whatever reason, I can feel it after. All the above symptoms appear again to various degrees.

This must have had an effect on my university studies, my productivity at work and my relationships with those around me.

I do not know how long term high levels of phe affect someone, but judging by how quickly a short term blip in diet affects me then I would say that they would be very detrimental. Perhaps meaning a person only fulfilling a fraction of their potential.

Q7. *[no response given to this question]*

Q8. *[no response given to this question]*

Q9. *[no response given to this question]*

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 51

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I am the mother of a now 27 year old PKU patient who has lived with PKU from birth. PKU takes over the lives of every family member, close and extended. Dietary compliance is key from birth otherwise brain damage will occur. My daughter grew up knowing nothing else other than a PKU diet. She learnt that she could only eat her own foods, that her food had to be weighed out to allow for the correct amount of protein and that she had to have foul tasting supplements. Life has been hard for my daughter and when she was a teenager she had to learn to manage the diet on her own, going to high school was a milestone.She has struggled with the diet for her whole life, more so when she was a teenager, rebelling and non compliance. Anxiety and depression kicked in at 17. Whilst it's wonderful that Kuvan will be prescribed for children, how can you expect anyone from the age of 18 to go from being on a normal diet to switch to a low protein diet? Coping skills will not exist, that life long education and support around the diet as it stands now, will not be there and will lead to psychological and physical damage. Who would want to suddenly stop eating 'normal foods' to go on this very restrictive low protein diet combined with supplements. It's a ludicrous suggestion and I challenge any one of the NICE committee to stop their own 'normal diet and try a LP one if only for a couple of days. NICE guidance states there should be a 'seamless pathway for (patients with rare diseases) transition from childhood to adolescence and on to adulthood and older age)'

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. My daughter has suffered from anxiety and depression and problems with her memory. As a teenager, she rebelled and ate foods which were 'forbidden' on the diet and also skipped supplements. Her phenylalanine levels were not always under control. And this is someone who has lived with a special diet from birth. My point is that if you ask someone who has been on a 'normal' diet from birth to suddenly stop and switch to

a LP diet, it will be very difficult and I believe that compliance will be very low. This will lead to a very high risk of brain damage (the brain can be permanently damaged over the age of 18) and high levels of anxiety and depression. In the long term this will cost the NHS more money.

Q5. When my daughter's phe levels are high, she feels very lethargic and her anxiety and depression are out of control. She finds it hard to get motivated and is very irritable. It's like a vicious circle, she knows that she should get her levels under control, but lacks the will and motivation to do so. This has affected her studies and led to her dropping out of university when she was 19.

Q6. Having high phe levels in the past, has definitely affected my daughter's future. She dropped out of university at the age of 19 as she found it very difficult to concentrate, was constantly tired and she had no motivation. This has led to almost a decade of doing jobs where she has had no chance of progression. This will inevitably have a knock on effect on future life experiences.

Q7. My daughter has suffered from anxiety and depression for almost a decade. As well as the medication she is on, she has had visits to psychiatrists and CBT sessions. She also suffers from IBS and has had a couple of colonoscopys. It seems very likely that these issues are related to her PKU. I know that this must have cost the NHS thousands in treatment and medication.

Q8. PKU has had a massive effect on my family since the day my daughter was born. As a parent of a PKU child, you focus so much more on that child than you do on your other non PKU child. Without realising, you deprive your other child of 'normal' activities, like having a desert when going out for a meal, keeping sweets or crisps in the house, baking normal food, as you don't want your PKU child to feel left out as they can't eat these things. I know now that my other daughter felt left out. I'm convinced that this is one of the reasons my 'non PKU ' daughter found it easy to move to Australia as she was very much left to her own devices and I feel a lot of guilt about that. As a parent all your focus is placed on your PKU child. You become over protective and find it hard to allow them to lead a 'normal' life for fear of them eating something they shouldn't . My own life was affected as I spent all my spare time after working full time every day, in the kitchen cooking 2 meals- one normal and one PKU meal from scratch (no convenience PKU friendly meals to be had!!) It even affected my relationship with my (now ex)husband as I spent an disproportionate amount of time focusing on PKU.

Q9. The PKU diet is very complex and difficult to follow. To expect people with learning difficulties to follow the diet with successful outcomes is almost impossible. There must be a level playing field here and Kuvan must be given to all adults to allow them to live a normal life without the added complications of a PKU diet.
Another group who should absolutely be given Kuvan are women who are planning to have a baby. It is crucial that their phe levels are kept very low (at the lowest level since infancy) otherwise the unborn baby has a very high chance of being damaged in the womb and being born severely damaged. The cost of giving Kuvan to pregnant women to enable a healthy and happy pregnancy (surely a basic human right)and to allow them to eat well (NICE strategy document for rare diseases) would be far less than having to provide life long healthcare for a baby born with abnormalities and learning difficulties to a PKU mother who has struggled to have such a pregnancy.

Q10. NICE should most definitely recommend KUVAN to help manage the risk of maternal PKU. All women deserve to have a happy and healthy pregnancy, but for a woman with PKU this currently is very difficult. The worry starts with the pre conception diet and having to get levels down to a safe level for conception. Keeping those levels low is crucial throughout pregnancy and this is a very worrying and anxious time, rather being a relaxed and happy one. It's also very difficult to eat well when your protein intake is probably the lowest it has had to be since you were a baby yourself. All in all, at least a year of stress and worry to ensure that you have a healthy child, free from brain damage, microcephaly, heart defects and low birth weight.

Q11. Allowing women of childbearing age to have access to Kuvan is crucial. I know that although my daughter uses contraception, she is constantly worried that this could fail and that because she is not planning to have a baby at the moment, should she get pregnant and an unplanned pregnancy would not lead to a healthy baby. The stress and worry would cause untold misery and heartache should the baby be born with maternal pku syndrome. You can't put a price on this, but the cost of treating the anxiety and depression of the mother, countless hospital visits and lifelong treatment for the baby would be so much more than the cost of Kuvan.

Q12. This should not be happening in 2021 when we have treatment within reach. Please understand that neurological damage to a child would cost so much more to the NHS than allowing of childbearing age to have access to PKU.

Q13. As I understand it, recommendations for Kuvan (Sapropterin) have been based on the cost of Kuvan itself. Once Bio Marin's exclusivity ends, generic versions of the drug will be available at a much cheaper cost. I would urge NICE to take this into consideration and reconsider their decision not to prescribe for all adults over the age of 18. Not to do so would cause untold damage and heartache.

Respondent 52

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. My child (****) with PKU is only 7 years old therefore I have no direct experience of dealing with a teenager with PKU. However, since the day my child was diagnosed 1 week after birth his condition has taken over our lives as a family. Not a day goes by when I, my wife and my daughter don’t have to prepare and calculate ****’s food and drink intake. As **** is recognised by the team at Manchester as one who may respond to the use of Kuvan, we are unbelievably eager to see what effect it will have, not just on his food intake , but his whole life. Should he respond and his daily protein intake increase, i couldn’t put into words how much this would improve his home life , his social life and his mental health. The underestimation people have of the effect of having such a strict low protein astounds me! If he responds well to Kuvan, it would allow him to eat out in a restaurant, negate the need to take his own packed lunch to his friends birthday parties, allow him to have a drink of his choice when visiting friends and give him that little independence of making his own choices when it comes to food. To remove this freedom on his 18th birthday and expect him to return to a hugely restrictive diet would not only be unethical, but would be verging on mental torture and I have no doubt would have an unspeakable negative impact on his entire life and those around him.

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. When my 7 year old son has high Phe levels we see a change in his behaviour. Although we are told none of this has ever been proven, we see increased stress and anxiety levels, agitation frustration and anger which I assume is caused by ‘brain fog’. His sleeping pattern becomes effected and he struggles to relax, which in turn effects his quality of life and those around him.

Q6. *[no response given to this question]*

Q7. We have experienced many things with **** which we are sure are linked to his diet and condition such as anxiety, stomach pains and constipation, muscle pains and fatigue. However, the clear number one issue is his mental health, when he feels ‘different’ to his peers at school and friends and wishes he could just be ‘normal’. We are so concerned these feelings are only going to worsen as he ages.

Q8. In our experience the stress levels of dealing with his condition are certainly not taken into account. The amount of time that has to be spent planning and preparing his food is much higher than you would expect. The challenge of attempting to add some variety to his diet is huge and adds huge amounts of pressure. Ensuring, he doesn’t consume (food or drink) goods he shouldn’t when at school or from friends is a huge concern as he ages. Dealing with him rejecting the meals we have prepared and planned then coming up with a plan ‘b’ is unbelievably time consuming and adds further challenges. Time spent studying the ingredients of food and drink in supermarkets when shopping approximately triples time it would take to do a normal shop.

Q9. **** is currently going through an evaluation process as teachers have shared comments regarding his behaviour in school and there are hints he may be either on the autism spectrum or have ADHD, both of which I think would hugely affect his ability to manage his diet on his own which concerns us hugely moving forward.

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. I don’t understand why they have provided a dosage limit for the amount of Kuvan to be prescribed. This is less than other countries who deal with PKU more effectively. I can only think this is linked to the cost of the product. It frustrates me that people who are making these decisions are simply looking at figures on a spreadsheet and budgeting based on the funds available and the number of people they can impact, rather than taking into account the human emotional factor which can change somebody’s life and allow them to live life and enjoy things which the majority of us take for granted. If a higher dosage could allow a person to live a life without supplements and give them freedom to eat a wide variety of foods, allow them ‘disappear’ into society rather stand out in most social situations and therefore have huge positive impacts on their physical and mental health, surely this should be a simple decision to make, although unquantifiable.

Respondent 53

**The responses are confidential and have been removed from this version of the document.*

Respondent 54

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I am a parent of an adult with PKU.
I am in favour of children having Kuvan if they respond but concerned at the proposal of withdrawing it at age 18. This is a time when young adults should be becoming more independent with many leaving home to study at university or for employment. My son struggled to manage his diet when he went to university and having to cope with an even stricter diet and a change in circumstances would have caused a lot of additional stress and anxiety to him and his family.

Q3. NICE's statements are contradictory

Q4. When my son was born we were told the diet could stop when he was 14 but as he grew guidance changed and now diet is recommended for life. Research is ongoing but there is concern about the possible long term effect of high Phe levels and even NICE is not certain about when brain development stops. Even if development does stop at around 25, will high Phe levels cause faster degeneration and health issues in the future?

Q5. When my son's levels were raised he found it difficult to concentrate and occasionally developed a tremor is his hands.

Q6. I do not agree. The impact of high levels varies on each individual but if possible effects are not considered it can result in poor quality of life, possible inability to maintain a job or live independently.
I do have concerns that having high Phe levels in the past could have an affect on my son's future health.

Q7. Fortunately the main healthcare costs relating to PKU for us were the regular clinic appointments, consultations with dietitians, GP appointments about prescriptions

Q8. caring for a child with PKU does put a strain on families. There is constant worry about maintaining Phe levels, extra time for organising prescriptions, planning meals, social events, holidays. Also siblings without PKU can feel resentful. An adult with PKU has the same concerns when managing the diet and many struggle to cope.

Q9. People who have extra problems managing PKU should not be penalised and be given as much support as possible to make it easier.

Q10. I believe that if a woman with PKU wants to start a family and responds to Kuvan, it should be available to her.

Q11. Don't feel able to comment on this

Q12. It would seem sensible to consider all possible costs that could result from uncontrolled PKU where Kuvan could have helped control.

Q13. My son was involved in the Kuvan trial. Recently the company has kept it's promise to provide the drug to those who participated but we're not sure for how long. This has made a big difference to him in managing his Phe levels . He can eat a lot more natural protein and feels much better in himself. The number of people who would be eligible is relatively small, even if all who are decide to use it. Generic alternatives should be available in the not too distant future which would probably result in a reduced cost. The figure quoted in the proposal paper does not include the discount referred to and some savings would result from reduced demand for prescription supplements and low protein products. It is also likely that easier management of the diet would reduce demands and the health service.
As my son said IT DOES MAKE A DIFFERENCE.

Respondent 55

**The responses are confidential and have been removed from this version of the document.*

Respondent 56

**The responses are confidential and have been removed from this version of the document.*

Respondent 57

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I am 58 years old, I have PKU, this rare condition has affected every stage of my life and becomes progressively worse as I get older.

Taking children off Kuvan at 18years old is heading for a disaster.

Teenage years were some of my most difficult, teenagers become self-conscious and have something to prove. If teenagers know Kuvan will be withdrawn at 18 years they will think what's the point, they will have no incentive and probably give up on the diet before they are 18. Everyone goes a bit "off the rails" and this will make it worse.

Cognitively they need controlled phe levels to do exams If you want to go to university or do well in your job you need good phenylalanine levels within the recommended range throughout your whole life.

I was advised by my clinician to come off the diet initially when I was 8 years old, Food began to frighten me, I struggled with PKU food and normal food. I felt so unwell I wanted to go back on the diet.

Going on and off diet meant my phenylalanine levels went up and down like a yoyo, it was mentally too difficult, too severe to cope with, I was overwhelmed.

I had to go to hospital to re learn doing the diet when I wanted to have a child. It was very difficult and confusing, it's a big thing to learn.

In my experience phenylalanine affects children's brains and adult's brains throughout life. This policy allows a childhood with controlled levels, by suddenly taking away Kuvan, higher levels will become a regular occurrence which will do damage .

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. In my experience I have definitely deteriorated over my adult years despite being on the PKU diet, all my brain function issues have become much worse, my eating disorder and my general health issues have become more severe.

I do not agree with NICE. I have a list of diagnosed mental and physical issues due to my PKU, they have all either developed or got much worse in my adult years despite doing the diet as best as I can.

Diagnosed with Major clinical depression associated with my PKU
Diagnosed with clinical Social anxiety associated with my PKU
Diagnosed with severe Eating disorder associated with my PKU
Diagnosed Personality disorder BPD, I think this is due to PKU but it is not proven
Psoriatic arthritis related to PKU
Fibromyalgia Pain related to PKU
Diverticulitis – bowel problem related to PKU
IBS related to PKU
Hiatus hernia – problem with stomach related to PKU
Reflux – related to PKU

The white matter in my brain has changed I have been told by my clinician this is due to high phenylalanine levels

Q5. All my mental and physical issues have an impact on my quality of life;

I cannot work because of mental health and physical issues due to my PKU. I have not worked for over ten years, not even part time.

I often have Brain fog, including lack of concentration, poor memory, very tired, major anxiety and depression

I have general poor health, joint problems, tremors and jerks. The jerks have got worse and they have started to happen unexpectedly.

For a long time people found it hard to be around me, I had jumpy thoughts, I confused people, I could talk but I was hyper and difficult to understand.

I started to get bad fatigue as an adult but it has got worse. When I was younger and working I had such fatigue I would sleep after work for

hours, my eating pattern would be affected making the diet more difficult, I had no energy and was quite ill with depression

I get lost a lot, I find it hard to find my way, I can't process simple journeys brain fog blocks my thinking, I still get lost going to my brothers' house, he has lived there for about twelve years, I still get lost every time I try to visit him.

I find it difficult to do stuff on a computer I have an Inability to sort things out. I can't apply myself and I get frustrated and annoyed with myself.

Q6. NICE definitely need to take into account the long term effects of high or low phe levels in adults.

I was told by my clinician to come off diet between the age of 8 and 22years my brain has been damaged and this has affected the quality of my whole life.

My relationship with food deteriorated when I was young, My eating disorders affect my ability to manage the diet leaving me with all the problems that come with high phe levels. My brain function and my physical problems have become progressively worse throughout adulthood. I cannot work, I rely on benefits.

I have had high levels in the past, this has had a long term impact, it also builds up over time as the problems accumulate. I am much worse now as an older adult than when I was a young adult.

I have to look after my disabled son who has cerebral palsy and West syndrome, he is peg fed in his stomach, he cannot do anything for himself he breaths that's it. He needs Complete total care.

It is Impossible to manage my own diet around his care I do have a carer for him but most of his care I do myself. Very stressful.

Q7. NICE should take the cost of my mental and physical problems into account for cost effective calculations.

Costs to the NHS to treat my problems are high. The provision of the PKU diet, prescription food and protein supplement is only one small part.

I have many mental and physical health issues due to my PKU. This makes it hard to manage the PKU diet and often gives me high phenylalanine levels. It is a vicious cycle.

I have loads of medication to take every day including daily Fentanyl Morphine patches for joint pain.
I also have two injections of Secukinumab cosentyx every 4 weeks, I believe this is expensive.

I have had loads of counselling throughout my life. I've done a few CBT courses but my learning problems make it hard to remember the strategies.

Other costs to the government include the benefits I receive. I have been awarded PIP and ESA at the highest rate. I would not qualify for these benefits if my health issues were not significant.

Q8. Through love my mum tried to do her best and felt responsible for my well- being. The diet was too difficult for her to do with me and she felt guilty and was very anxious. She was afraid of doing things wrong. She was worried she would be blamed for my health not going well.

My daughter and son help me now, all the time. They help with practical things like paying bills, managing money is hard for me. They help with cooking for me too.

Q9. Any additional issues in your life makes the diet much harder or impossible to manage. Many adults with PKU are disadvantaged because of the symptoms of their PKU. The eating disorders, the regular brain fog that turns into consistent brain fog, lack of concentration, the depression, the anxiety etc all make the diet too difficult. It is immoral that people today are not getting the help they need. Keeping people on track with the help of Kuvan would stop them developing serious mental and physical problems like me.

Everyone with PKU is at risk of developing really serious expensive problems that accumulate throughout adulthood. NICE has not considered this, they are totally wrong and are not listening to us, NICE have completely misunderstood the effects of PKU on adults.

Q10. Nice should be recommending that women with PKU need extra care from pre conception and provide services for women even before they are thinking of starting a family. The thought of having a child is very frightening if you have PKU.

Help before, throughout, and after pregnancy is crucial and if new treatments like Kuvan are safe and help mums keep their phe levels lower then it should be highly recommended.

If women all over the world are already using this drug it must be safe in pregnancy. It would have helped my experience of pregnancy.

Mentally it is very difficult, especially as hormones are added into the mix along with all the PKU difficulties. The diet can feel impossible to get right.

Q11. As young girls we know we have to go on a lower exchange diet. I was petrified of pregnancy as a teenager, how was I going to tell a potential partner?

The responsibility of keeping your unborn child safe is terrifying and I found it overwhelming at times. You worry so much that if your phe levels are raised, which happens even if you are doing the diet as good as you can, it feels like everything is your fault.

When you become pregnant you get a strong bond with the unborn child, everything you eat is potentially bad for the child. I couldn't work out exchanges very well. Struggled with confidence, overwhelmed by the responsibility. I had a lot of anxiety, I was scared, and unsure, it was a

long journey.

I had three miscarriages, I lost three potential babies, PKU makes it so much harder, its extra extra tough to even get pregnant on a PKU diet.

Before I had my first son who is disabled I did the diet as well as possible. I don't know why my son is disabled, I wanted to have a reason but it was proven not to be PKU.

I went on to have a daughter and another son who are healthy and not disabled.

When my first son who is disabled was born I had to come off diet in hospital I didn't want to come off diet I knew It would make me feel unwell.

Going on and off diet is too severe to cope with, its overwhelming, mentally too difficult. I had lots of aspects to deal with, very tough after already losing three babies.

It was an emotional and mentally stressful time, one minute on the diet, then off diet. Awful time. I was very, very angry when I was trying to accept my disabled son. I resented other healthy children. Coping was hard, PKU affected my ability to cope.

If Kuvan helps to keep blood phe levels lower and is safe then it would have made my pregnancies so much easier, safer and happier.

Q12. The costs of preventing neurological damage in babies of PKU mums must be taken into account. The cost of looking after a disabled child is huge both emotionally for the family and financially for the NHS.

Q13. I feel like a ginea pig, my difficulties have been recorded to benefit the younger ones. My generation have already paid the price to develop and establish the diet for life.
I did what I did for everyone coming up behind me. I deserve to benefit from new treatments too.

I would like my difficulties in pregnancy to be listened to so other young women do not have to go through what I have been through. People with PKU need support and care throughout their whole lives. If there are new treatments available everyone who could benefit should have access. In the long run the damage PKU causes can destroy lives and becomes even more expensive to the NHS.

Respondent 58

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. It is vital that Kuvan is continued after the age of 18. This is a very important time when PKUers are off to University or work, going out with friends eating and socialising. It's a huge transition from being under parents care and control of the diet the person is out there on their own. Kuvan would be a huge help. Throughout an adults life, things get harder, more responsibilities etc.. It's even more important to stick to the diet. If not a downward spiral occurs. The wrong things are eaten and it's even harder to pick yourself up and get the diet under control. Depression sets in. If your depressed you eat, that's bad for the PKUer. Kuvan would allow the adult a little more flexibility too allow for these ups and downs in their life and the ability to keep control of the diet and their lives.

Q3. I do not agree with NICE's view

Q4. I can't comment on brain damage but I know it seriously affects concentration, which affects, work, daily activities, driving etc.. Brain fog, thinking through everyday problems, memory. All of this results in a yoyo diet.

Q5. I agree with this, also see above.

Q6. Yes, I totally agree. How can a PKUer function properly with life and work when they have confusion, can't concentrate are tired etc..?

Q7. Depression issues are a problem, having time off work to visit the doctor, also tiredness at work can lead to loosing your job.

Q8. A huge impact on the rest of the family. Choice of holidays, always self catering, hotels are too difficult. Wherever you go, always having to take PKU food. Every 24hrs is based around the PKUer. Every meal is based around the PKUer.

Q9. High levels of PKU cause many problems and issues. Surely the cost of all the special foods that PKUers need by prescriptions eg. Flour, pasta, milk substitute, etc.. would outweigh the cost of Kuvan.

Q10. I cannot comment on this.

Q11. I can not comment on this.

Q12. None

Q13. No more comments.

Respondent 59

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Children having Kuvan is brilliant, then taking it away at 18 is cruel. Learning how to manage diet as a teenager and then an adult, independently, is difficult. It has been the hardest thing I've had to try to do and I still struggle. Mentally and physically we are still developing when we are 18 and older- to sabotage people by taking away effective treatment is cruel and dangerous. It is not fair. PKU affects our body and brain- our whole existence. Personal, social, academic, professional life is all affected by our PKU, our health, our diet. To sabotage teenagers when they are starting university, at college or beginning to work, or making other life choices as they enter adulthood, is disgusting. My health has been deteriorating due to lack of decent treatment for PKU- my academic ability is altered, my ability to work has stopped, my social and personal life is difficult, and I am always stressed and in pain due to diet. I had to deal with the emotional challenges of having my

expectations of treatment drastically alter in my teenage years- it is extremely difficult to navigate in myself, it is more difficult to explain to employers, to explain to college, to even explain to GPs when I needed help. Just because PKU is rare does not mean we don't deserve treatment. To put 18 year olds in the position of fighting for their health- cognitive, mental and physical, is shocking and I am sure will lead to many many problems that the NHS will then have to deal with through various treatments in the future for that person.

Q3. I do not agree with NICE's view; NICE's statements are contradictory

Q4. My cognitive ability has changed throughout my educational career. I was very intelligent, focused, with a high IQ and earning top scores for school work. During college, when I was now told to be off-diet (therefore my blood phe levels increasing, which is what would happen when coming off Kuvan) I was unable to concentrate, struggled to engage or remeber informationa nd really struggled to focus on my exams. Now I am in university again and I have noticed such a decrease in my ability to focus, even read, that I have been given Disabled Student Allowance for tools and mentoring, extra time for assessments as well as being identified as deserving PIP. I now have PIP for daily living allowance- due to the difficulties I have do to changes in my cognitive abilty and mental wellbeing. This is a result of PKU- physically and also emotionally, it is extreemly difficult to manage PKU as an adult when my treatment was altered in my late teens- as NICE proposes to do to 18 year olds. As a young adult I have developed a twitch and chronic stress, chronic fatigue and chronic pain. I struggle to talk, to use my mouth, I become clumsy and dropsy. I have chronic brain fog- It is a huge struggle to focus to write this, I don't think I could go back and edit it. I have more to say for all of these answers, it is difficult to express myself- this struggle has developed during adulthood.

Q5. The listed symptoms affect my daily life. I also struggle to drive, to socialise, to go outside to complete tasks like shopping, etc, often. It is extremely difficult to maintain blood phe levels as everything seems to affect them, yet the only treatment we have to try to control them is inadequate as well as extremely difficult to do. Some days I had to forgo my diet and my health in order to complete work/employment- this led to complete burn out, of which I am still recovering. High levels cause pain and discomfort, feelings of being upset and irritable- this affects social relations. It affects my memory- I struggle to remember important short term things, but I also have no recollection of what should be happy memories- this also affects relationships and the strength of relationships, this has a negative affect on my feelings of security in friendships, feelings of belonging and connection- because I have forgotten many of our shared expereinces. Luckily, we realised this- that I am missing memories- and so I feel less upset, thinking i wasnt involved, and friends feel less offended that I have forgotten great times. I struggled to do my a level exams because i couldnt remeber things. Infact, the most memory loss is around my late teenager years when my treatement/diet was being changed. I high extremely intense feelings, I become hyperactive of mind yet cluggish of body - I am often feelings frustrated and overwhelmed. This does make daily life difficult to manage, to enjoy, to cope with. Everything takes a long time to organise - even nipping to the shop, or to walk the dog- because if i dont afford the time and energy and mental capacity to organising i may forget to eat, to have supplement or become too tired and hungry- and my phe levels increase and i become very unwell quickly.

Q6. Extremely so, I am costing the nhs and the country more as a PKU diet with inadequate treatment. I have been on anti-anxiety medication recently and have been advised to return to using anti-anxiety medication. The point of the meds is so that I can keep my phe-levels in a healthy range because the stress and panic induced by the difficulty of the low protein diet treatment for PKU is so immense and difficult and i am not coping. I was in employment from my teenage years until 32- I am not unemployed, receiving universal credit and PIP due to the impact of adult PKU and the difficulty of the PKU diet. In recent years I have had the help of counsellors, well-being support worker and an employment advisor. I need to see my GP often due to problems with anxiety, panic, cognitive paralysis, liver issues now, weight issues. If I get pregnant I will need a lot of extra support from the NHS. I feel like I am quickly and drastically becoming more unwell. Physically and mentally and I am realising that I deserve treatment and support. At this rate, I fear that I won't be able to work again and will have to remain on benefits for life. I have always been a hard worker, a dedicated team mate, I have my skills and a lot of experience and intelligence. I can work extremely well and be a valued member of a team, loyal and social- but I am becoming more and more unwell. The mental toll of PKU diet for life is destroying me mentally and physically, the PKU symptoms are destroying me mentally and physically and I think I will need a lot more support. It is extremely depressing, and feels like it is wasting my life. I feel sabotaged. I am losing my independence. I think I was developing agoraphobia- I was becoming paranoid out in public. I burnt out and had to leave my job - unable to do anything. PKU prescription food is difficult to obtain and organise, and eating out/grocery shopping/cooking can be extremely difficult and distressing.

Q7. extreme anxiety, gut problems which I am unsure of what they are yet, liver problems developing (non-alcohol related), constant weight gain, chronic fatigue, chronic pain, chronic brain fog, depression, twitches, hyperactivity, nerve pain, dermatillomania.

There are significant healthcare costs related to living with PKU- I need treatment for this issues that I have ignored for many years due to the ignoring of PKU, now they are all severe and increasing in severity. There is possibly more that I am needing. I am losing my independence, and I am 34. See above too.

Q8. Definitely. I am 34 and have constantly needed support from my family. I was struggling with the symptoms of PKU so much whilst working that my Mum had to prepare my morning supplement and food. I still often need help physically with preparing food, remembering food, supplements, care, treatment, self care, prompts. Family or friends are often supporting me when out in public. I struggle to organise and am very forgetful so I need help to do many things, and rarely am in charge of things alone- when I am I make mistakes. Emotionally I need a lot of support, reassurance, practical help, care, patience. My family or whoever I live with need to live with my mood, irritabilty, hyperactivity, symptoms. I have had to come live with my family again as I needed support practically, emotionally, mentally, financially. Prescriptions is so difficult to manage that I need support with that.

Q9. to not allow adults treatment is DISCRIMINATION. Especially the identified groups above and any other aults who are disadvantaged in some way. The longer I am living as an adult with PKU with inadequate treatment the more impairments I am living with, the lower my income is (my family has always been low income). It is discriminatory to deny kuvan to adults and it is putting pku people at risk to take them off kuvan at 18. There is costs to living with PKU for the NHS, for the individual and to the country- low protein diet is advised for LIFE now, so how is that ever going to be less cost than childhood? We will still need prescription food and supplements , and a longer time to struggle with symtoms or develop more.

Q10. Kuvan should be available to women who are trying to have a baby and pregnant and post natal. Kuvan should be available to all adults. Kuvan should be available to any one who may become pregnant. Mental health and maternal health are important in pregnancy- to value a fetus over the mother is grossly discriminatory, and to value neither mother nor baby is also discriminatory.

Q11. It is scary to consider pregnancy. I have felt for a long time that I am 'not allowed' to become pregnant due to the difficulty of maintaining good phe levels- this has had a negative affect on my mental health and self worth. I have felt like I would be shunned by doctors if i became pregnant due to my PKU and how hard it is to maintain good phe levels. I feel like I would not be adequately cared for if i became pregnant. I worry that I cannot become pregnant due to my PKU symptoms and care and how I was abandoned by medical care at 16 and the problems that have developed since. It feels discriminatory and unfair, it is a very emotional topic- i feel unequipped and unprepared for pregnancy, i feel lik ei will be shunned and judged and punished if i become pregnant. it is scary and deeply upsetting. I also feel that my adult life is unworthy- it matters less than the potential fetus I may carry- as the potential fetus I may one day carry has been cared for more than my adult self was cared for. I feel abandoned and like i can not ask for help or support regarding pregnancy.

Q12. It seems like NICE know that there is information that would support adult access to kuvan, yet are actively avoiding it in order to not allow it for adults. I think that's foolish and short-sighted. The effects of PKU on adults will highly likely affect their parenting- increased stress in daily living being a simple example.

Q13. My response is messy and emotional- I have not got the capacity to edit, refine, to come across 'well'- it is taking all of my mental energy and effort to be able to do this today. I feel anxious that I am coming across unreliable as I am emotional, may sound depressed, confusing- but this is the result of my PKU for me right now. I suffered burn out at the beginning of 2019- I was really suffering for years, and trying to get help for my PKU. I am still struggling to heal from my burn out and find better ways to be, but I am still struggling to cope. I know that I have forgotten a lot fo what I would like to say, things that would be pertinent and effective. I am struggling, and I have been for years now. I am losing the abilties I had- cognitively, mentally, physically. I wish to not feel brain fog. I wish to not feel nausea. I wish to not have food anxiety. I wish to have access to the range of PKU treatment that is already in use in the world. Why are we behind?

I wonder why NICE think adults should not have kuvan- why people should have it taken away when they are 18. It is cruel that there has been this treatment for so long, a third of my life, yet we are continually denied it. It is short-sighted to only give children the chance of better treatment, especially as those children will also be denied kuvan when they are at an age where they will be entering employment, family life, adulthood. I feel unfortunate that I am continually missing out on PKU treatment, and it hurts that so many others are too. The glimmer of hope that is being given to children to have kuvan ... I don't understand why it will be taken away at 18. I don't understand why adults are no longer worthy of treatment. We have been waiting years for this treatment for PKU- more treatments are in use in other countries- other conditions are treated in the UK at a very high expense. Why don't we matter? Living with PKU, for me, is extremely exhausting- the hopes that keep being dashed throughout my life have drained me. I was a vibrant, intelligent, happy, friendly child and I have been struggling more and more as I get older. I feel lost and almost hopeless to ever live without the debilitating brain fog that is stopping me from so much right now. I do, and have done, everything that I can to be well. I have followed all advise throughout my life about treating my PKU. I feel used and abandoned. I do not want children to feel this depleted. Half promised of treatment, hopes being dashed, is soul crushing- and this is on top of the already difficult reality of living with PKU and struggling to keep blood phe levels within a good range. Exhausted. I am so drained- without better treatment I see very little hope of me not costing the NHS a lifetime of prescription food and medications, would I ever be off PIP? Will I ever have the capacity to work again? I am genuinely scared for my health and abilty- and it feels so cruel, because my whole life, my family and I have followed the NHS's advice regarding treating and living with my PKU. I am even considering being a part of human trials for gene therapy, as it feels like it is THE ONLY way I could get any treatment for my PKU. I would have to put y life on hole for 5 years- no allowance of pregnancy for 5 years- I am 34 now. It is a scary position that I feel the only way to have any treatment for my condition (of which there are a number of safe treatments out currently, kuvan being well used for many years) is to become a human guinea pig and trial a new, untested, gene therapy. I have been living in fear for years- that I am killing myself by everything that I do or no not eat. The fear that I am killing myself if horrible, I feel helpless- because the PKU diet for life is too difficult, and treatment is available but I am not allowed it.

I'm thankful for the treatment I had a child and the support I have from my dieticians now, but I feel extremely let down by the lack of access to innovative treatment that is already being safely used already in the world.

Respondent 60

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. People should be given anything that is going to be able to benefit them for their life space. On the whole it will be cheaper (eg medication, hospital visits, gp visits, prescription food, etc, especially regarding mental health, physical health, carers, etc...)

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. I am witnessing a daily drain on my daughter's brain that is taking it's toll on her physically and mentally, because she is aware of it and there seems to be nothing she can do to make it go away. It is damaging and the longer it goes on I feel that it will only get worse. She finds it very hard to plan a future because she doesn't know what what she will be like in the future- for example, having kids, long-term relationships, anything. She can't plan anything because her brain can't take it in or see beyond the end of the day at times. This is different from when she was younger.

Q5. Totally draining. Unable to do ANYTHING. Very very upsetting for my daughter- there are things she wants to do, and needs to do, but can't even begin to think how to start them. Because of that she gets very very depressed.

Q6. Knowing how high levels affected my daughter when she was younger, older and now, of course they affect you. The proof is how my daughter is how she is- when her bloods are in good range, she has more life, she can see further ahead. The longer the blood levels are higher, the bigger the impact they have.

Q7. As a mother I am very concerned daily, it does affect my own mental and physical health as well as my daughters. Seeing my daughter deteriorating in front of my eyes and there appears to be nothing that I can do. Of course there are associated costs- NHS supplements, medication, food, counselling, dieticians, recompense for travel to clinic, carer, time missed from work to help daughter function or attend important clinic/meetings. My mental health as a mother/carer, my physical health. Carers' allowance and other benefits, eg she is on PIP and UC as she cannot work.

Q8. Absolutely. We have the experience and we see things in the PKU that they are unable to see in themselves. It affects the whole family. We all look out for her, including her sibling. The whole family is affected, holidays, days out, unable to visit extended family due to meals. The household often centres around the PKU.

Q9. How is it fair to not support adults with PKU in these groups. Measuring supplments and managing a diet for life is very complicated- it is simpler and cheaper and less daunting and upsetting to be able to have kuvan.

Q10. If women had kuvan from childhood and throughout adulthood they can make decisions better. To struggle with having kuvan taken away, and then managing the extremely difficult pre-con diet, is a hugely difficult task that could damage mother and baby mentally and physically.

Q11. My daughter is child bearing age- I would be relieved that she could have Kuvan. I want her to have it because to not have it despite it being available is unnecessarily making her suffer greatly.

Q12. This is an extremely relevant cost to account for. It is a cost of adulthood PKU, why is it not accounted for? The cost of this runs from when the women is wanting to become pregnant, throughout. This could be a cost that runs for years, and is a direct cost of PKU adulthood.

Q13. Kuvan is available and should be used in the UK. It has not been done before, so it needs to be done now. In the long run, the cost of giving Kuvan will be a fraction of the cost of no one able to have kuvan.

Every PKU person should have access to kuvan. The benefits of treating PKU people will come so we need to have kuvan.

Respondent 61

Q1. It is great that children will receive treatment but unfair that adults will not.

Q2. The plasticity of the brain is established in neurology, we know that the brain continues to grow and make new connections throughout a person's lifespan. Knowing this, and applying it to PKU, there is no safe age where we can remove treatment and permit chronic brain damage.

Much in a person's life changes at 18, leaving home, starting a career or going to university. This is not the time to suddenly require a teenager to eat 1/6th of the protein they had previously be able to eat. This is a dramatic amount which would remove whole food groups, e.g., dairy, cheese, egg, tofu, high-protein vegetables, ordinary bread, baked goods, legumes, beer!

The effect on the brain just when embarking on career or further education will have life altering effects. The effect on social life, of suddenly not being able to eat with friends, will be devastating. I can tell you first hand that busy bar staff are not interested in having a discussion on aspartame levels in their sodas at 9pm.

At 18, just when you are proposing ending the supply of Kuvan, I was in my first year at university. My university hall offered breakfast and dinner, supplying lunch was up to us. I had to go to university accommodation team with a letter from a metabolic specialist explaining the critical need for a bread maker in a student dorm room. All the dining room staff at lunch and dinner knew me by name because there had been a department wide conference about me before the year started. Try blending in with your peers after that.

Representations from my GPs, clinicians, and family had all been made to assure the staff that I wasn't a danger to their business, that I could be fed with only a few tweaks to their menus. Even then, I spent a year living on boiled vegetables and water (the cheapest cordial juices all had aspartame). Of course, all my fellow students knew this, my food was a constant topic of conversation. "Can't you just eat meat and then throw it up later?" Eating disorders are common in PKU, even if there has been no funding for a study into it.

Early careers were difficult, I worked in a physical environment which required a high-energy diet. Unlike my colleagues, I couldn’t refuel with a high-protein meal of meat, or fish or eggs at lunch and then have a kip. Because my diet must be low-protein, I had to spend my entire lunchtime eating huge amounts of prescription pasta. And it never filled me up. There is only so much stomach you can fill, and I was always running out of energy and hungry in the afternoons. Several jobs were unsustainable because of my inability to maintain high levels of energy throughout the working day. In my twenties, I had to leave jobs because the lack of food available to someone with PKU meant I physically couldn't do the work.

Q3. I do not agree with NICE's view;NICE's statements are contradictory; As noted, brain damage can occur at any age.

Q4. At the age of 34 I received a brain injury, a bleed in the brain which was initially mis-diagnosed as concussion, during an amateur football match. During my NHS supported recovery, I found that many of the symptoms of diagnosed brain damage, high anxiety levels, headache, difficulty with co-ordination, brain fog, were the same as those I experience with high phe levels.

The damage to the brain is the same regardless of the mechanism or the age of the patient.

Q5. As I noted above, the effects of high Phe levels are the same as the effects of brain damage. Because it is brain damage.

As I note in my response on the physical and mental effects of PKU, clinicians consider my PKU diet to have been well controlled for 40 years. And yet I still experience the symptoms of brain damage due to PKU.

Symptoms of brain damage experienced under a well controlled diet:
Headache & migraine
Lack of co-ordination
Tremors
Reduced executive function
Reduced logical thought capacity
Brain fog
High anxiety levels
Low energy levels

Poor physical recovery after illness or exercise
Depression
Increased social isolation

Q6. I do not agree.

There is a need for calculating cost-effectiveness of all treatments on the NHS, and such calculations must include the cumulative effects of a disease.

Alzheimer's disease causes long-term damage to the brain which result in the symptoms of brain injury. If there were a cure for it, would NICE dismiss the long-term effects of the disease when considering the cost-effectiveness of any treatment?

No. The whole point of the treatment is to prevent brain damage and avert these long-term effects. Therefore the cost of long-term effects must be considered when costing the treatment.

It is the same with PKU. The cost of treating the long-term effects of brain damage caused by PKU, and the cost of lost opportunities and earnings to the individuals, families and wider society must be taken into consideration when calculating the cost-effectiveness of all treatments.

Q7. My PKU diet is considered to be well controlled and my blood levels are within in the EU guidelines. PKU clinics in both NZ and the UK have repeatedly described me as their 'star patient'. I am allowed 5g of natural protein per day, which is one slice of wholemeal bread.

Despite this incredibly tight limitation, my family and I have worked exceptionally hard over the past 40 years to manage my PKU. This required considerable expense, as PKU friendly foods in the supermarket always cost more. Then there is the need to consider the lost time spent micromanaging food and the lost opportunities, places and people I simply cannot be with because I can't eat and survive there.

The costs of the PKU diet and its effects must be included in any cost-effectiveness study because it is a prescribed treatment for an inherited metabolic disease. This means that all monetary, physical and mental costs, including those not currently covered by the NHS, must be considered. Food is used as a treatment for PKU, therefore the cost of food is a healthcare cost.

From a monetary perspective, the cost of PKU friendly foods is a massive burden. The NSPKU have reported the cost to the NHS of the prescribed foods to be up to £16,000 per patient every year. Families and individuals with PKU must spend considerably more than the average food bill for PKU friendly food in supermarkets. In my examples below, I show that individuals and families with PKU must spend two to four times more simply to eat. All costs are from Sainsbury's, a mid-level supermarket.

Example: KoKo coconut based plain yoghurt (160g is 1phe) costs 40p/100g at Sainsbury's. That is four times more than the cost of normal plain yoghurt, which I cannot eat through no fault of my own.

Example: Milk, an everyday essential item. I compare Sno-Pro (prescribed for PKU on the NHS), coconut milk and regular milk:

Sno-Pro: paid for by NHS but contains Phe. If you have more than 3/4 of a cup per day (not just on your morning cereal, you need to measure your coffee & tea, meals, sauces, baked goods...) it must be counted in the Phe allowance.
Coconut milk: £1 per litre. I am allowed to have two cups of this before I need to count it in my meagre Phe allowance.
Regular milk: 50p/litre for semi-skimmed, but half a cup would wipe out all my Phe allowance for a day.

Again, I have to pay at least double what a normal person would simply to have milk.

Not only are PKU individuals and their families forced to pay far more for a basic essential like food and drink, they are also having to spend far more time and energy planning out their diet for the week. Someone with PKU must know what they want for dinner on Thursday when they do the weekly Saturday morning shop. During that shop, every person with PKU must make those calculations which I laid out above for every single item which they buy.

We need to know what we are having for dinner before we can sit down to eat breakfast, so we can ensure we don't exceed my allowed Phe. There is no room for spontaneity with restricted diet therapy. A simple treat of a single biscuit with your morning tea means you must completely rethink your lunch, afternoon tea and dinner too. Or you will increase the damage to your brain.

Surveys by the NSPKU shows that this planning takes about 20 hours per person per week. That is as much as a part time job. A part time job which could be spent earning income and contributing to society but which is instead spent on just being able to eat.

The restricted PKU diet causes physical harm too. My diet was naturally low in omega fish oils when I hit puberty. This was in the early 90s and there was far less awareness of the contributions DHA make to ligament and skin repair. My ligaments did not have all the nutrition required for my growth spurts, and it was my achilles tendons which suffered. They didn’t grow along with the rest of my body and I had to spend six months with my ankles in bandages. Six months is a long time when you are 12, and this led to further social isolation in schools and play.

To prevent this from happening again, my metabolic clinic advised me to take fish oil tablets daily. I have done so for 30 years at a personal cost of £60 per year. That is £1800 on a single item required because the treatment for an inherited disorder is a diet which removes 85% of food.

I have been an active sportswoman, playing football and other team sports all my life. However, because of this early PKU induced injury, my achilles tendons are still a chronic and painful concern. So are other tendons in my knees which haven’t been able to repair correctly following injury. My ability to recover physically following a football match or other exercise is markedly worse than my non-PKU team-mates, even with a diet under careful control. My skin is covered with scars from periods of low nutrition or high Phe levels when quotidian cuts and injuries didn’t fully heal.

Mental health isn’t as obvious as a scar, but PKU is detrimental to that too. Consider that we live in a society where food is seen alternately as a weapon or a medicine, a panacea or the cause of all illness. You need only glance at newspaper headlines to see how much judgement is cast on ordinary diets. Food can be classed as ‘healthy’, ‘un-healthy’, ‘processed’, ‘non-processed’, ‘natural’, ‘junk’…

Now consider that the current treatment for PKU is all about controlling what you eat. I have lived with PKU for over 40 years and am an active member of the PKU community. I go to conferences, clinic days, cooking demonstrations and I have never met anyone with PKU who doesn't suffer from food anxiety. I include myself in that group.

We are forced to be anxious about our food. Food is a clear and present threat to anyone with PKU. But we need food to survive and food is an integral part of all societies and cultures. We are automatically excluded from so many rituals and celebrations, Christmas dinner is a burden not a joy. Try living with that and not having mental and social complications.

At the age of 11 I missed out on 100% in a science test because I was unable to identify a substance. It was milk. Because I had never been able to touch, drink, or smell milk, I was unable to identify it. This was a single mistake in a single test, which I happen to know about because I asked the teacher afterwards. This mistake clearly occurred because of my PKU. But in the last 30 years, how many other tests have I failed, or opportunities have I lost, or mistakes have I made, or social occasions have I missed because I carry this burden through no fault of my own?

And living with the uncertainty, anxiety, and frustration of those losses, well, it's like what everyone else has had to live with during this first year of a pandemic. Only this is for a lifetime.

Q8. I am one of three children and neither my brother nor sister have PKU. But they have been affected by it. As children, they were not allowed the same snacks as their friends and because they might give them to me. They were not allowed to bring home party bags in case I found the bags and ate the treats. Because of this, they experienced social exclusion too. They weren't invited to their friend's parties because their sister would come and dealing with her diet was just too difficult.

My brother and sister were teased in school because of their "weird sister, the one who drinks vomit". (One day my dietary supplement spilled in my bag and the entire cloakroom stank of it. It stank like vomit, so for my entire time at school I was the kid who drank vomit.) My brother and sister would spend time in detention for fighting off kids trying to hide worms in my sandwiches. "We can make her eat meat." "She drinks vomit, she can eat worms too!"

We seldom went to restaurants, even on family holidays. When we had to eat out, we would walk the streets of unfamiliar towns trying to find something, anything, which might be suitable for PKU. Once we found somewhere, my mum and dad wouldn't order their meal until they were certain that the restaurant staff could make my meal. We sat through lots of confused negotiations with maitre d's while embarrassing queues formed behind us.

My husband suffers now, and not just because my cooking and baking has to be experimental (deep-fried banana blossom and chips!). All restaurant dinners, takeaways, pub meals, motorway stops, presents and gifts must be PKU friendly. He misses out on social occasions, meals, treats, and gifts because I am not able to eat them. He never complains, but he shouldn’t have to miss out.

Q9. When thinking of the cost-effectiveness of all treatments for PKU, it must be acknowledged that poor compliance results in a very high risk of people with PKU acquiring a cognitive impairment or learning disability through brain injury. So yes, those already with a learning disability or cognitive impairment will find it harder to stick to a restricted diet. But also, by not providing non-diet therapies to assist with compliance to the PKU diet there is a risk of inflicting such an injury which would then make further compliance with diet harder.

As illustrated in my previous replies, adherence to the PKU diet costs 2-4 times more than someone living on a normal diet. This is in addition to any help offered by the NHS. For this reason, anyone on a low income will have greater difficulty in adhering to the PKU diet. This has further cost implications as lower adherence leads to greater difficulty in education and career. This in turn results in a lower contribution to society from the PKU individual which leads to a lower income which leads to poorer adherence… Kuvan and other non-dietary treatments for PKU would provide great assistance in stopping this cycle and result in greater well-being for the individual who can in turn give more value to society.

Finally, to address the elephant in the room, brain damage from high Phe levels still occurs beyond 18 years of age. Removing treatment at that age is a clear discrimination against adults.

Q10. Kuvan and other non-dietary treatments should be available for maternal PKU

Q11. When I was sixteen, medical textbooks listed an alarming range of conditions and injuries common in babies born to mothers with PKU. They ranged from a 50% increased risk of brain damage, microcephaly, and heart disorders to a lower increased risk of learning disabilities. This was one of the main reasons for my decision not to have children.
Those dangers have not disappeared.

Yes, we now know more about how to avoid poor outcomes and there are better prescription foods available as well as more support in clinics for women with PKU who wish to have children. But those risks, those considerations for future parents are still there. Kuvan and other non-diet therapies would clearly help mothers to reduce the danger to their children. They should be recommended for maternal PKU.

Q12. This is an obvious oversight. Neurological damage to children of both controlled and uncontrolled PKU is a clear danger. There are obvious moral and ethical implications of ignoring neurologically damaged children. Beyond those implications, the costs to society in healthcare, specialised education, support in future careers and the opportunity cost of the things which that person might have achieved and contributed to society simply must be considered in any cost-effectiveness calculations.

Q13. The draft guidance noted a dearth of scientific data on PKU and the effects & burdens of restricted diet therapy. That this has been overlooked in research until now is not the fault of patients. If NICE needs more evidence to make judgements, then support the research for such evidence.

Kuvan, or rather sapropterin, is no longer in patent and cheaper, generic versions are available. Why were these cheaper options not considered in the cost-effectiveness for this draft guidance?

As further evidence of the burden which the restricted diet therapy of PKU places upon individuals, families and society, I offer this final observation. I have now spent five hours and over 3,000 words arguing for access to a treatment for a disease where food actually kills brain cells and maims lives.

Respondent 62

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I find this part particularly concerning. I have been on a diet for 40 years and find it difficult to maintain. I would find it extremely difficult to have freedom with the diet and then suddenly restricted in an important part of life. Starting going into exams at school and then university that requires stable levels of protein that helps concentration and memory for revision. Not to mention trying to maintain a new type of diet and the social aspects that come along & also no parental support while at university.

Q3. I do not agree with NICE's view

Q4. I do not have any first hand experience of brain damage. I do understand the risks of not staying on the diet. Which are drilled into you at an early age.

Q5. I agree with these comments. Which makes me question the reason why it's withheld for adults? I have classic PKU and am only on 10 grams of protein a day. Some days that I am too hungry and I have to go over my levels which is not ideal as I have to maintain levels for my job as I am a Biomedical Scientist. Also I have cook most dinners from scratch. I would like one of the Nice employees to stay on a diet of 10 grams of protein a day. While drinking 3 supplements a day which is just about palatable. In other words if I am trying a new improved supplement and it doesn't make me throw up then it's great.

Q6. I worry about getting dementia earlier in life. Due PKU only starting to be treated 20 years ago. I don't think there is enough evidence due to the treatment of PKU advancing soo much.

Q7. As I am only on 10 grams of protein I have to take 3 supplements a day and rely heavily on prescription foods (biscuits, pasta, rice, bread, bread flour, cake flour).

Q8. I do think that they should take into account the impact of PKU. I was at a birthday party when I was 8 years old & couldn't eat any of the food so my mum had to bring my own food with me. Very embarrassed and left. I only felt confident about talking about my diet in my late 30's.

Q9. My diet is manageable and I am on 10 grams. I do think adults who are on at least 5 grams of protein should be considered for KUVAN.

Q10. I don't know

Q11. I think it should be available for women who want to have a baby.

Q12. I do think that this should be considered

Q13. No

Respondent 63

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Some adults cannot manage the diet or suppliments and never will be able to high levels of Phe stops their brains functioning properly.

Q3. I do not agree with NICE's view

Q4. Yes you can see them losing the ability to do things they could in the past and ask you the same question a dozen times as they cannot remember it.

Q5. I am a 71year old Grandmother of twin boys aged 20 years old both have PKU and have lived with me and their two older sisters since school age as their Mother could not cope and had a mental breakdown due to the strains PKU and diet put on her.

High Phe levels affects all levels of life in over 18's as they cannot take information or instructions and keep them to carry out simple tasks. Their irration and fustration can cause bad tempers and outbursts of anger sometimes even physical strike outs against members of the family.The diet restricts them from eating out with friends or family and social activities which takes them away from home for any length of time all of this severley impairs their quality of life. Many employment oppotunities are above their capabilities due to high Phe levels and diet.

Q6. Yes they suffer sickness, headaches and unable to fill out a job application to achieve a basic level of employment all of which stop them from fulfilling a meaniful life now and in the future as well.

Q7. PKU and diet as caused one of the twins to have severe mouth ulcers which can stop you eating and drinking without constant pain feeling sick with bouts of stomache pain they can lead to Chrones desease which needs investigating in hospital and as been done twice already this means possible further investigations in the future and treatments.

Q8. It is extremely difficult to be the bad person insisting they drink their suppliments and eat the correct food leading to arguements and confrontation when the rest of the family are eating normal food it makes you feel guilty and upset so often which leads to others in the family having mental health problems with depression being the main reason for lack of self worth. Some mothers break down completely and cannot take the responsibilities which means Grandparents and siblings have to be the carers instead.

Q9. No because all of these people deserve the best treatment possible and cannot stand up for themselves especially those with learning disabilities which some have been directly caused by the refusal of Kuvan to stop the high levels of Phe which resulted in their brain damage.

Q10. Give them a fighting chance with Kuvan as all dietitians agree a good healthy diet is the best way to allow the unborn child to develope healthy. Mothers will suffer mentally if their PKU as affected the childs health and future.

Q11. The fear of your child being harmed or born with problems because of you is unacceptable when help is available.

Q12. When a child is born with neurological damage is for the rest of their lives from the very start the costs are high to matain support, carers, schools, social workers and medical needs.

Q13. A diabetic adult would not be refused insulin to control their sugar levels it is unthinkable and so is refusing adult PKU suffers from medication that could improve their lives. There are many more medicines that cost large amounts and have been approved. I have waited 20 years for my Grandsons to have Kuvan and believe the quality of life should be the most important thing that is considered we are not a third world country.

Respondent 64

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. As a 25 year old adult with PKU, who has experienced how being off diet, I know how difficult it is to try to go back to a normal PKU diet. I have struggled especially as a female getting ready for the pre conception diet. Letting these children try Kuvan and having a more normal diet will eventually make it really hard for them to stick to the PKU diet if you then take it off them at 18. A PKU diet is recommended for life not just for while you are a child.

Q3. I do not agree with NICE's view

Q4. Speaking to other PKU patients have been told of relatives of theirs who have come off PKU diet and have had cognitive problems which started in their adulthood and have continued throughout their life.

Q5. Having high phe levels can really effect your mood, I know from experience that I have had really low times and I get annoyed by the smallest of things which normally wouldn’t bother me.

Q6. *[no response given to this question]*

Q7. I have found at times being really low in mood because I find it really difficult to loose weight due to the PKU diet and having to take the protein substitutes. I find it is much harder to find low sugar, low calorie foods that good well with a PKU diet and the exchanges allowance for the day.

Q8. Yes I do. PKU affects the whole family. When you want to celebrate occasions, it’s quite hard to find PKU friendly restaurants and foods when out and about. I found that I had to have a lot of side dishes which affected my family because they felt guilty for me not eating a proper meal. Also, having to buy different foods is an extra cost when do the weekly shop.

Q9. As a female who is looking to start the pre-conception diet within the next couple of years, I am beginning to learn about what that entails. I will have to restrict my food even more than what I do now on a regular PKU diet. I am already finding this hard. As a pregnant woman who has cravings I can’t see how this will get any easier. Having to restrict yourself to very few exchanges a day is really challenging because something as simple as bowl of cereal can already be 2 exchanges of maybe half your exchange allowance for the day.

Q10. *[no response given to this question]*

Q11. The thought of having a baby whilst having PKU makes me incredibly anxious due to the risks not monitoring your exchanges can have on your baby. I want to know that I can have a safe pregnancy but that is not guaranteed with PKU. I’m nervous about what I might eat because already struggle with my choices now on a greater number of exchanges per day.

Q12. I have not had a baby but I have been thinking about the pre-conception diet. I know that if my phe levels are not in control it can have massive affects on my unborn child. I think this cost should definitely be considered to help pregnancy become a better experience for women.

Q13. I really think as a person who has had PKU stopping Kuvan for patients at the age of 18 is going to make the lives of these patients extremely hard. Restarting a full PKU diet is honestly one of the most difficult things I have ever experienced. Two years after restarting my diet, after being off diet just four years, I am still finding it challenging to get back into routines and not eat what I shouldn’t. Diet is recommended for life and I wouldn’t be able to have a baby safely and without life long development issues if I did not have follow the diet. At 18 this is the age where people move out of home to go to university and start life, if patients are expected to start a PKU diet and not have Kuvan, there is a good chance these young adults may not be able to have the support of their families if they have moved away. I have struggled with PKU diet, but it would have been impossible without the support of my family. PKU is for life not just when you are a child.

Respondent 65

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I grew up alongside someone with PKU and as an adult in her thirties she has more issues with PKU now in the form of fatigue and struggling to concentrate than ever before. As a child the diet was difficult but doable. She has over 30 years of experience of managing this through diet and yet it effects her more now than ever. If this drug can help then it should definitely not be stopped at 18. It should be available at all life stages whenever anyone is struggling with PKU.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. I have noticed a huge difference in how this effects my friend. They are no longer able to work due to fatigue and bran fog. It caused lots of problems with their job when they were struggling. It has massively effected their quality of life as an adult and it makes me really upset that there's a drug that could help but they can't access it.

Q6. Of course they should be taken in to account. They effect someone's ability to work, maintain relationships, hobbies and quality of life in general.

Q7. *[no response given to this question]*

Q8. Yes absolutely. PKU effects the entire family.

Q9. *[no response given to this question]*

Q10. I think they should recommend this possibility be investigated.

Q11. *[no response given to this question]*

Q12. It should be included

Q13. *[no response given to this question]*

Respondent 66

**The responses are confidential and have been removed from this version of the document.*

Respondent 67

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. No. The PKU diet is difficult enough to follow without the added complications of a making a huge adjustment to the way it will need to be managed when a child reaches the age of 18.

Q3. NICE's statements are contradictory

Q4. I have first hand experience of increased Phe levels leading to diminished cognitive capacity, albeit this appears to occur only temporarily.

Q5. High Phe levels definitely contribute to an increase in my tiredness, forgetfulness and irritability and have been thought to also lead to a feeling of general unwellness.

Q6. My diet was better controlled as a child and I excelled throughout school. As I grew older and controlled my own diet I found academia increasingly difficult and my achievements became average rather than exceptional:

Q7. In my experience there are no significant healthcare costs associated with PKU.

Q8. PKU has an impact on partners and children, especially in respect of social gatherings involving food.

Q9. PKU diets are particularly expensive and I believe there will be a significant impact upon lower income households. There is also the potential Impact upon a PKU sufferer if their parents lack the ability to maintain a PKU diet due to their own educational and/or cultural experiences. In addition I have seen at close quarters the difficulties experienced by couples planning a family due to the extreme levels of dietary control needed prior to conception and throughout pregnancy.

Q10. Kuvan should be available to pregnant women and women trying to conceive.

Q11. Kuvan should be available to pregnant women and women trying to conceive.

Q12. The failure to include these costs appears to be negligent and should be included

Q13. The evidence appears to be at best incomplete and at worst tailored to achieve a specific predetermined outcome. This needs to be corrected.

Respondent 68

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. It would be incredibly difficult for an 18 year old and their parents to get to grips with the full PKU diet when there would be no previous experience of it and it's complexities once someone hits 18 years of age and has been exposed to 'normal' foods. There would be very little incentive for them to get into the diet until it's too late and symptoms and issues would come to light.

Q3. I do not agree with NICE's view;NICE's statements are contradictory;Your statement and decision on long term brain damage in adults caused by PKU is completely contradictory in terms of medical research and as a support worker within medical research I completely disagree with your view. If medical research says brain development continues until at least 25 years of age then why are you producing documents that state otherwise?

Q4. *[no response given to this question]*

Q5. When my Phe levels are higher than they normally are, I struggle to concentrate at work and can only do menial tasks, I have to leave other tasks and complex processes for another day because I cannot focus/have brain fog. I only have milk PKU, for most cases of classic PKU this would be exasperated and much more noticeable, and probably affect career choices and quality of life in the long run. I am lucky.

Q6. *[no response given to this question]*

Q7. The protein substitutes alone are very expensive and are needed 3 times a day. Because people with PKU cannot get enough calories from fruit and vegetables to get through their day we have to reply on prescription foods which range from pasta and rice substitutes to pretty disgusting tasting yogurts and dry biscuits. The range is limited and only produced by a small range of companies. When I was last 'on diet' (I have a mild extremely rare form on PKU which mean I only have to be on this diet whilst pregnant or trying for a baby-to keep the baby's development safe) my GP surgery continuously made me feel guilty and like I was putting them out needing the medication and prescription foods as part of my days to days life. No one seems to have considered these on going costs to normal PKU patients which continue throughout their lives, let alone the additional medication and costs to the NHS for issues that surround PKU such as mental health support, stomach digestion issues and insomnia which are commonplace in the PKU community. Please calculate these costs in order to make a fair decision as to whether Kuvan is in fact cost effective otherwise you have zero argument against it.

Q8. The stress the PKU diet placed on my partner whilst I was pregnant was enormous. He was trying to buy and cook the correct food for me, weigh everything out - and I mean everything - work full time and the overall worry for my health and the baby's was massive. It was the most stressful part of both of our lives so far, and further complicated by additional complications which were picked up in our baby's 20 weeks scan potentially due to managing PKU.

Q9. *[no response given to this question]*

Q10. I'm sure there is evidence of this somewhere, otherwise pregnant women PKU could eat what they want and there would not be a worldwide suggestion that PHE levels should be considerably less than the normal day-to-day levels. Please do your research properly before disallowing Kuvan for pregnant women. Pregnant women and women trying to conceive should have access to Kuvan to support the physical development of the next generation.

Q11. I will tell you about my experience with PKU and being pregnant. Please also bear this in mind for when an 18 year old experiences the diet for the first time.
As someone with a very mild form of PKU I picked up the diet from scratch at the age of 35 when my partner and myself decided we would like to start a family. The best of incentives. I received the very best medical support from the specialists at my local hospital in Bristol and was very lucky with my situation. It became clear that this was going to be a bumpy ride very quickly.
WHen I first started the diet I was shocked to discover that I could not eat normal sliced bread for breakfast, pasta, rice pretty much everything I was used to other than fruit and veg. I started weighing everything that went into my meals and calculating the protein content which I had to adhere to -18 grams a day, down from around 70grms. I lost 3 kg in a couple of weeks because I did not know how to feed myself. The weight kept coming off until I had regular phone call assistance from my dietician essentially telling me what to eat.
After a couple of months my PHE levels were constant and safely low. I was lucky that I became pregnant quickly. The morning sickness and faintness that came with the first trimester was very difficult, I had no appetite for food and yet if I didn't ingest and keep in enough calories and my protein supplements my PHE levels would increase and then the baby's development would be put in jeopardy, especially the heart, brain and nervous system which relies on low PHE levels in the blood to develop normally. If a pregnant woman at this stage of pregnancy cannot keep down enough calories and protein supplements her PHE levels in the blood will go up and affect the baby's development, if she can't do this due to hyperemesis gravidarum, the woman has to go into hospital to be on a drip until her PHE levels return to a safe point. I wonder how much that costs the NHS?!?
At the point of my 20 week scan I was told that my baby had a heart defect. The guilt that came with this devastating news was unbearable. At the time I was working full time in a full on role, trying to manage the PKU and all the additional medical appointments that came with a PKU pregnancy and to be told that despite all my hard work my baby had a heart defect was completely heart-breaking. I blamed myself, there is no complete evidence that it was my PHE levels which affected the development of my sons heart but that is something I will never know and always question. If Kuvan had been available I would not have had to work quite as hard controlling my diet and maybe this would not have happened.
We got lucky, and by the time my son was born he only had a small hole in his heart, he is being closely monitored but has escaped having heart surgery. He is now a strong 16 month old and I am a much more anxious and guilt ridden person who will always question whether there was something she could have done differently to have hindered that hole in his heart from developing.
Kuvan should be available to all, however if you are going to limit it to children then this should include unborn babies who should not pay the price for the medical difficulties that their mums have of bringing a baby into this world in the first place. Give Kuvan to pregnant women and women who are trying to conceive, this will ensure the next generation have the best start and limit the medical costs of things when they go wrong.

Q12. My son's heart condition has required multiple additional ultrasounds, heart scans and doctors and surgeons appointments. I have no absolute evidence that his condition was caused by high PHE levels during pregnancy but hey would not have been picked up otherwise. These costs have not been calculated as a saving if pregnant women had access to Kuvan whilst they were pregnant and while they are trying to conceive. Therefore your estimated costs are for Kuvan are 'out'.

Q13. Please review this again soon due to the patent running out for the branded product Kuvan, there will be other products on the market very soon and the PKU community do not deserve to wait another 3-4 years for medication which other countries have had access to for 12 years.

Respondent 69

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I am the sister of someone with pku. I know from experience that pku is a LIFELONG struggle, and to take away treatment at a random age is cruel and non sensical. My sister was told as a child she would only have to follow the diet until 12, they then changed this to 18, and then with more research they discovered that diet and medication needs to continue for life. However, she had already been distanced from help and was told she could stop, she continued her supplements but had massive struggles regarding diet, her cognitive function and mental health. At 18, childrean are still PKU and still majorly impacted every day by their condition. Kuvan is a right, it is a treatment that can provide normality to a difficult life. it is hard enough for people who have never had kuvan to maintain diet and treatments for pku as is, so it would be more cruel to let kids have this and then take it away. It is completely irresponsible to take away peoples necessary medications once they hit 18, as they will suddenly be plunged into a massively confusing world of diet ad medication to a level they are not used to. It is both cruel and inhumane to take away vital medication for a lifelong condition, this condition does not go away with age. PKU is a damaging condition that if not controlled perfectly causes major issues with health and cognitive function, even with brilliant monitoring and diet, phe levels can rise drastically. To take

away medication randomly from someone and expect them to maintain an impossible diet in the hopes their blood levels remain safe, is irresponsible, cruel, and disgusting and is setting them up for failure and life long damage.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. My sister has made sure to consistently have her supplements and maintain diet as well as she can, however her cognitive abilities are being greatly impacted and impaired from damage of phe. These issues are scary and are happening quickly. She is a bright woman, yet she is losing her ability to function with regular things. Noises are too much to process, her thoughts are jumbled, and she is having difficulty to vocalise her thoughts. She has written her experiences down already, but because of the damage from Phe levels, she forgot to add some of her major experiences from PKU, including losing large amounts of hair(balding) and losing large amounts of muscle mass.

Q5. High phe levels reduce my sister, and cause her distress often. Brain fog is practically a constant and many things make it worse. Her memory is awful and is getting worse and she is terrified of this and lives her every day scared about how quickly her brain is deteriorating. She is constantly tired and drained, and has little to no energy, even to do day to day tasks like showering and getting up. I have to constantly be on guard and help her as her energy levels are depleted, and her memory issues result in her forgetting to eat, and even when she remembers, it is massively difficult for her to figure out what to have, and is difficult to think of food that wont make her symptoms worse. My sister experiences massive mood swings and can be frustrated and angry very easily, this is due to her phe levels and issues regarding PKU. She is constantly in pain and emotional distress, and can feel irritated and upset often.

Q6. High phe levels have been shown to create large amounts of white matter in the brain and it has been noted that it also causes stroke like symptoms. this has also been observed in my sister. Damage recieved from high levels of phe are permanent and distressing, and can happen seemingly out of nowhere. Maintaining diet is not a surefire way to avoid raised levels. High and low levels of phe are both damaging, and playing a costant balancing game is unfair and cruel for people. the cost of failing this balancing act is damage to the brain, and it is near impossible to maintain consistent levels. Having high phe levels impacts you later in life, as seen with my sister. In the time she was struggling with =out much help with her Pku, her levels were high and she was taking major damage to her cognitive abilities, this has near destroyed her memory both long and short and means that loads of her memories are gone.

Q7. My sister has had to have medication regarding the extreme depression and anxiety caused from pku, yet due to how they impacter her phe levels she is having to find a new medication more suited. She also has liver damage which has also been seen in other people with PKU and will need treatment regarding this. Her pku has caused muscle weakness and deterioration and she is now on medication and vitimans to try help with this, she has to buy many vitamins. My sister is also unable to work and is now having to recieve benefits to help her as her symptoms worsened to the point where work was impossible, this caused major distress and financial issues. She is on disability because her Pku has caused issues to the point that she needs major help, and me and my parents take care of her.

Q8. I am the younger sister of a woman with PKU. My entire life PKU has dominated the focus for my family. I help my sister maintain diet and I cook and plan food when she is unable to process what to have, which is often, with help from our mother. My sister cannot go to appointments alone due to the emotional distress caused, and due to her appointments having to be in Birmingham, she cannot go that far alone. She often does not feel safe to drive so my mother drives her, and if that is not possible I travel with her on the train, however this is causing more and more distress to her, and it is difficult to get the hospital. my family all make sure she has her spheres(supplement), and eats regularly, we also try to not upset her or put her under any stress as her mood is easily impacted. I listen out when she showers and baths as there have been times she has fallen or zoned out for long portions of time.

Q9. NICE has decided to disregard the entire pku community as they believe it would be easier. Women who decide to conceive have massive difficulty trying to get such a low level without kuvan, and people of a low income cannot afford the things that make pku easier. All groups within pku face difficulty, and giving a cinsitent and simple treatment of kuvan, would reduce all the other costs from the effects of no kuvan.

Q10. NICE should actually research the impact of raised phe levels to babies in the womb. Kuvan would massively improve the phe levels and safety of the baby, and also the mental and cognitive health of the pregnant woman.

Q11. My sister has had doctors talking about her having babies and how strict and dangerous is could be to the baby since she was also a child. The amount of planning it takes to even consider having a child is massive with people with PKU as they have to reduce their PHE levels to a near impossible level and maintain this. The damage to baby and mental state can be huge, and this is only taking into account women who plan to get pregnant. Women who fall pregnant have a scary moment, where they must immediately drop their phe levels which can be both difficult and dangerous to mu=other and child, and even then they do not know of what damage they may have already caused. Having women consistently on Kuvan would take away this risk entirely and would result in no other extra costs.

Q12. At least half of the PKU population are women, of which many if not most will want children, and all have the right to children. This is a massive group of people to not take into account. The costs to prevent neurological damage to the children should be taken into account. There would be the costs of consistent appointments and travel prior to conception, as the phe levels and all medical levels would have to be monitored and corrected, the cost of any more medication including more supplements, medication for mental health, and vitamins and medications for general health, and then upon getting pregnant, the cost of more appointments, any more necessary medications and any treatments if things go wrong. If damage does arise to the child, their would be huge costs medically for treatment, and help for the child and mother, and if there was any failure from the doctors, this could easily lead to malpractice cases to be dealt with.

Q13. Nice has to take into consideration the cost of all things people with PKU have to have to maintain even a semblance of normality in their life. Kuvan through life would be a consistent and smaller cost for a greater result.

Respondent 70

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. This decision is incredibly unfair for anybody living with PKU. I cast my mind back to being a child with PKU and remembering all the things my Mam taught me about the condition such as foods I could or couldn't eat. What exchanges were, When to drink my supplements, how important it was not to go over my daily intake of exchanges and the effects this could have on my health. I learnt more as I grew and developed the skills to live with such a restrictive diet. The skills I learnt I have since been able to put back into practice after coming off diet when I was a teenager.

Around 15/16 years of age is when I began to cheat on the diet and skip my supplements or even meals here and there as I was coming to the end of my school education and beginning a new chapter in life of 6th form college. As college was like a whole new world for me personally I wanted to do all the things my friends did. This included going to the canteen and eating whatever food was on that day, not taking supplements and generally just having the freedom to socialise and not worry about PKU. Plus of course I was studying quite hard and as I was cheating on the diet I began to notice I felt I was slower at getting work done and found it harder to concentrate. Still I wasn't ready to make the connection with these feelings and being off my PKU diet. Around the age of 18 is probably when the whole PKU diet went out of the window. I wasn't taking supplements at all and was now old enough to drink alcohol which again is something me and friends would do socially and with that came late night takeaways and eating all the wrong food. Life for me around this age, and I think for any typical 18 year old was at its most chaotic and full of change. This is a time when my PKU was completely overlooked.
In the years to follow I would begin employment in catering and struggle further with long busy days being off diet and not taking supplements. The sad thing is I was mentally in a place where I couldn't see the wood for the trees. I felt like I was underachieving in everything I was doing and less capable than my peers. These feelings brought anxiety and depression as well as total social withdrawal at times. I did receive NHS treatment for Depression and Anxiety in my Mid Twenties and still wonder if this would have been needed if I was on PKU diet at the time. Or if the anxiety and depression would have not been so bad.
fast forwarding to now I am back on my PKU diet and feeling a lot better in myself. I now work full time in an admin based job role within the civil service and find that I can only fulfil my potential within this role when I am on diet. This can be a struggle day to day and I do have to batch cook meals every Sunday to keep my bloods low throughout the working week but for me its worth it as it keeps me at my best. I guess the point I am trying to make is without the skills I learnt from being a child with PKU I would have found it near enough impossible to go back on diet myself. Also as a teenager with PKU when I was off diet and levels were sky high it took me many many years to actually be able to identify the reason I was feeling as bad as I was even though it was staring me in the face. High levels are like living on the outside of life and seeing days go by but not actually feeling or remembering being a participant in them. It really is an awful way to feel and one that you can't actually understand unless you have PKU and are able to go off diet and be fortunate enough to come out the other side.
Kuvan has the potential to change the lives of every single person living with Phenylketonuria for the better. To give a child a chance at living life without a massively restrictive diet and having all their cognitive and executive functions working to their best and clarity of thought is an amazing thing. However to have that all cruelly ripped away from them at the age of 18 and have to feel their brain and body decline as well as taking away the freedom of eating whatever they want which they have had for 18 years is a devastation I feel I would never want to happen to myself or indeed any adult with PKU. My dietician once said I could try Kuvan as part of a clinical trial as it would be funded I was so excited until I learnt that the Kuvan would them be taken away again after the study. I declined the offer after learning this. I'd rather not have Kuvan at all than have it given and then taken away entirely. It would be the cause of a mental health crisis for me personally and I think anyone who would experience this.

Q3. NICE's statements are contradictory

Q4. I feel very lucky that I do not (to my knowledge) have long term brain damage. I think NICE do need to look into this further and work out why they have contradicted themselves within their statements.

Q5. High PHE levels effect every aspect of a persons life. I personally feel tired, confused, useless, self conscious of responses in front of groups of people. I want to stay away from people entirely. I forget things I would usually do everyday without thinking if my levels were not high. If my bloods are high I find it very hard to make decisions, even simple decisions. I usually feel so low about myself that I feel myself withdraw entirely. If my levels are high I can become unaware of myself and unintentionally eat the wrong food or even forget to eat foods or take my supplements. I feel I can't work very well in my job when my levels are high. I get very irritable about loud noises to the point of irrational anger. Light exposure becomes very uncomfortable as it hurts my head and hurts my eyes.

Prescription food can cause sickness and stomach upset requiring further treatments and medications.

Q6. I disagree with this as it is necessary. For me personally having high PHE levels has took its tole on my quality of life both mentally and physically. Mentally I felt less capable to do my work at school, college and work. This caused a great deal of anxiety and depression for me which I had therapy for when I was around 25 years old. I have had counselling, cognitive analytical therapy as well as cognitive behavioural therapy throughout my life. I have also been on medication for these conditions which again is a further cost for the NHS. One which may have been avoided if my PHE levels were not high.
Physically I have felt exhausted and even ended employment in jobs where I did not feel I was physically capable of working in. I have also had ongoing back problems since the age of 18 years including discectomy surgery at this age and ongoing back problems. I have had stomach problems throughout my life. Again more medication required to deal with these problems.
If Kuvan was made available for all people with PKU maybes these kind of experiences and expenses for the NHS could be avoided entirely. One thing that is certain is the expenses of supplements and prescription foods for people with PKU and the NHS would be greatly reduced.

Q7. Throughout my life I have had treatment and medications for anxiety, depression, gut problems and pain problems. This includes pain killers, anti depressants, therapy for mental health, medication for stomach problems. As well as many ongoing tests and monitoring of all these ongoing health conditions. I have also had had my brain analysed to see if there were any lasting brain damage effects as a result of being of diet for so many years. (Newcastle RVI)

Q8. After speaking with my Mam today she explains that she had a lot of difficulties with mine and my brothers PKU management when were kids such as:-
babies supplements had to be made by hand from any different elements of things (Vitamins, minerals, protein and non protein)
Preparing meals in advance for school.
measuring and weighing foods accurately.
If PKU children became poorly their levels would spike and they couldn't take supplements.
Ordering and receiving prescriptions correctly.
Us bedwetting due to drinking so many supplements throughout the day.
Physical and mental exhaustion.
My mother used to eat out the way of us as she felt guilty that we couldn't eat it.
Special occasions felt unfair.
Watching us very closely in case we ate the wrong foods.

As we got older we became hungrier and still couldn't eat enough.
Fighting with doctors and chemists for more prescription foods.
food costs.
Feelings that children would be removed from mothers care if not properly looked after.
A kind doctor took my Mam to see another PKU mother to see older PKU children who were healthy and well to make her feel better.
Unable to eat meals as a family.
Separate food menu's.
Problems with her own mental health.
Relationship difficulties.
Feelings of guilt towards other non PKU children in terms of them not getting the same level of attention.
Physical health conditions.
Mental health conditions. (anxiety, depression)
Not being able to afford healthy and low protein food i.e. fresh fruit, free from foods.
Fear of children missing out on social events and educational events.
Missed opportunities at school.
Worries over child mental health and physical health.
Overlooking her own mental and physical health in order to care for her own children.
Lack of support and understanding from schools, teachers.
Going without certain things in order to ensure we had all the things we needed.
Fighting for Disability Living Allowance for us for many years and not being able to find work for herself as she was a full time carer for her 2 PKU children.
DLA being awarded and taken away again even though PKU is a lifelong condition.

(Again these are also more costs on society that may be able to be avoided with the use lifelong use of KUVAN as DLA can still be claimed for PKU adults)

Q9. This decision is completely unfair on these people. These people have been overlooked entirely. Further consideration has to be taken in this matter. These people need as much support as possible.
Saying it is not possible to recommend KUVAN to these people due to the cost effectiveness in adults is almost like saying we acknowledge these people need the medication but they basically can't have it anyway. Ridiculous.
This is one of the most inconsiderate and unfair statement I have ever read.

Q10. NICE need to be presented with medical evidence and facts before they can look further into this. They need to do more research and speak with as many PKU mothers as they can to gather all the information they require before they can make an informed decision. I myself am I PKU male and so is my brother so unfortunately my knowledge in this area is limited.

Q11. My knowledge on this subject are limited. What I will say is if Kuvan can prevent a mother from being mentally unwell and requiring treatment for this as well as preventing a child being born with severe disabilities and requiring life long care then surely the cost saving in this scenario out weighs the cost of Kuvan entirely.

Q12. Unable to comment.

Q13. If any further information is required from me please do not hesitate to contact me.

********** (PKU adult age 30)

Respondent 71 (appears to be a duplicate of respondent 70)

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. This decision is incredibly unfair for anybody living with PKU. I cast my mind back to being a child with PKU and remembering all the things my Mam taught me about the condition such as foods I could or couldn't eat. What exchanges were, When to drink my supplements, how important it was not to go over my daily intake of exchanges and the effects this could have on my health. I learnt more as I grew and developed the skills to live with such a restrictive diet. The skills I learnt I have since been able to put back into practice after coming off diet when I was a teenager.
Around 15/16 years of age is when I began to cheat on the diet and skip my supplements or even meals here and there as I was coming to the end of my school education and beginning a new chapter in life of 6th form college. As college was like a whole new world for me personally I wanted to do all the things my friends did. This included going to the canteen and eating whatever food was on that day, not taking supplements and generally just having the freedom to socialise and not worry about PKU. Plus of course I was studying quite hard and as I was cheating on the diet I began to notice I felt I was slower at getting work done and found it harder to concentrate. Still I wasn't ready to make the connection with these feelings and being off my PKU diet. Around the age of 18 is probably when the whole PKU diet went out of the window. I wasn't taking supplements at all and was now old enough to drink alcohol which again is something me and friends would do socially and with that came late night takeaways and eating all the wrong food. Life for me around this age, and I think for any typical 18 year old was at its most chaotic and full of change. This is a time when my PKU was completely overlooked.
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fast forwarding to now I am back on my PKU diet and feeling a lot better in myself. I now work full time in an admin based job role within the civil service and find that I can only fulfil my potential within this role when I am on diet. This can be a struggle day to day and I do have to batch cook meals every Sunday to keep my bloods low throughout the working week but for me its worth it as it keeps me at my best. I guess the point I am trying to make is without the skills I learnt from being a child with PKU I would have found it near enough impossible to go back on diet myself. Also as a teenager with PKU when I was off diet and levels were sky high it took me many many years to actually be able to identify

the reason I was feeling as bad as I was even though it was staring me in the face. High levels are like living on the outside of life and seeing days go by but not actually feeling or remembering being a participant in them. It really is an awful way to feel and one that you can't actually understand unless you have PKU and are able to go off diet and be fortunate enough to come out the other side.
Kuvan has the potential to change the lives of every single person living with Phenylketonuria for the better. To give a child a chance at living life without a massively restrictive diet and having all their cognitive and executive functions working to their best and clarity of thought is an amazing thing. However to have that all cruelly ripped away from them at the age of 18 and have to feel their brain and body decline as well as taking away the freedom of eating whatever they want which they have had for 18 years is a devastation I feel I would never want to happen to myself or indeed any adult with PKU. My dietician once said I could try Kuvan as part of a clinical trial as it would be funded I was so excited until I learnt that the Kuvan would them be taken away again after the study. I declined the offer after learning this. I'd rather not have Kuvan at all than have it given and then taken away entirely. It would be the cause of a mental health crisis for me personally and I think anyone who would experience this.

Q3. NICE's statements are contradictory

Q4. I feel very lucky that I do not (to my knowledge) have long term brain damage. I think NICE do need to look into this further and work out why they have contradicted themselves within their statements.

Q5. High PHE levels effect every aspect of a persons life. I personally feel tired, confused, useless, self conscious of responses in front of groups of people. I want to stay away from people entirely. I forget things I would usually do everyday without thinking if my levels were not high. If my bloods are high I find it very hard to make decisions, even simple decisions. I usually feel so low about myself that I feel myself withdraw entirely. If my levels are high I can become unaware of myself and unintentionally eat the wrong food or even forget to eat foods or take my supplements. I feel I can't work very well in my job when my levels are high. I get very irritable about loud noises to the point of irrational anger. Light exposure becomes very uncomfortable as it hurts my head and hurts my eyes.
Prescription food can cause sickness and stomach upset requiring further treatments and medications.

Q6. I disagree with this as it is necessary. For me personally having high PHE levels has took its tole on my quality of life both mentally and physically. Mentally I felt less capable to do my work at school, college and work. This caused a great deal of anxiety and depression for me which I had therapy for when I was around 25 years old. I have had counselling, cognitive analytical therapy as well as cognitive behavioural therapy throughout my life. I have also been on medication for these conditions which again is a further cost for the NHS. One which may have been avoided if my PHE levels were not high.
Physically I have felt exhausted and even ended employment in jobs where I did not feel I was physically capable of working in. I have also had ongoing back problems since the age of 18 years including discectomy surgery at this age and ongoing back problems. I have had stomach problems throughout my life. Again more medication required to deal with these problems.
If Kuvan was made available for all people with PKU maybes these kind of experiences and expenses for the NHS could be avoided entirely. One thing that is certain is the expenses of supplements and prescription foods for people with PKU and the NHS would be greatly reduced.

Q7. Throughout my life I have had treatment and medications for anxiety, depression, gut problems and pain problems. This includes pain killers, anti depressants, therapy for mental health, medication for stomach problems. As well as many ongoing tests and monitoring of all these ongoing health conditions. I have also had had my brain analysed to see if there were any lasting brain damage effects as a result of being of diet for so many years. (Newcastle RVI)

Q8. After speaking with my Mam today she explains that she had a lot of difficulties with mine and my brothers PKU management when were kids such as:-
babies supplements had to be made by hand from any different elements of things (Vitamins, minerals, protein and non protein)
Preparing meals in advance for school.
measuring and weighing foods accurately.
If PKU children became poorly their levels would spike and they couldn't take supplements.
Ordering and receiving prescriptions correctly.
Us bedwetting due to drinking so many supplements throughout the day.
Physical and mental exhaustion.
My mother used to eat out the way of us as she felt guilty that we couldn't eat it.
Special occasions felt unfair.
Watching us very closely in case we ate the wrong foods.
As we got older we became hungrier and still couldn't eat enough.
Fighting with doctors and chemists for more prescription foods.
food costs.
Feelings that children would be removed from mothers care if not properly looked after.
A kind doctor took my Mam to see another PKU mother to see older PKU children who were healthy and well to make her feel better.
Unable to eat meals as a family.
Separate food menu's.
Problems with her own mental health.
Relationship difficulties.
Feelings of guilt towards other non PKU children in terms of them not getting the same level of attention.
Physical health conditions.
Mental health conditions. (anxiety, depression)
Not being able to afford healthy and low protein food i.e. fresh fruit, free from foods.
Fear of children missing out on social events and educational events.
Missed opportunities at school.
Worries over child mental health and physical health.
Overlooking her own mental and physical health in order to care for her own children.
Lack of support and understanding from schools, teachers.
Going without certain things in order to ensure we had all the things we needed.

Fighting for Disability Living Allowance for us for many years and not being able to find work for herself as she was a full time carer for her 2 PKU children.
DLA being awarded and taken away again even though PKU is a lifelong condition.

(Again these are also more costs on society that may be able to be avoided with the use lifelong use of KUVAN as DLA can still be claimed for PKU adults)

Q9. This decision is completely unfair on these people. These people have been overlooked entirely. Further consideration has to be taken in this matter. These people need as much support as possible.
Saying it is not possible to recommend KUVAN to these people due to the cost effectiveness in adults is almost like saying we acknowledge these people need the medication but they basically can't have it anyway. Ridiculous.
This is one of the most inconsiderate and unfair statement I have ever read.

Q10. NICE need to be presented with medical evidence and facts before they can look further into this. They need to do more research and speak with as many PKU mothers as they can to gather all the information they require before they can make an informed decision. I myself am I PKU male and so is my brother so unfortunately my knowledge in this area is limited.

Q11. My knowledge on this subject are limited. What I will say is if Kuvan can prevent a mother from being mentally unwell and requiring treatment for this as well as preventing a child being born with severe disabilities and requiring life long care then surely the cost saving in this scenario out weighs the cost of Kuvan entirely.

Q12. Unable to comment.

Q13. If any further information is required from me please do not hesitate to contact me.

********** (PKU adult age 30)

Respondent 72 (appears to be a duplicate of 70 and 71)

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. This decision is incredibly unfair for anybody living with PKU. I cast my mind back to being a child with PKU and remembering all the things my Mam taught me about the condition such as foods I could or couldn't eat. What exchanges were, When to drink my supplements, how important it was not to go over my daily intake of exchanges and the effects this could have on my health. I learnt more as I grew and developed the skills to live with such a restrictive diet. The skills I learnt I have since been able to put back into practice after coming off diet when I was a teenager. Around 15/16 years of age is when I began to cheat on the diet and skip my supplements or even meals here and there as I was coming to the end of my school education and beginning a new chapter in life of 6th form college. As college was like a whole new world for me personally I wanted to do all the things my friends did. This included going to the canteen and eating whatever food was on that day, not taking supplements and generally just having the freedom to socialise and not worry about PKU. Plus of course I was studying quite hard and as I was cheating on the diet I began to notice I felt I was slower at getting work done and found it harder to concentrate. Still I wasn't ready to make the connection with these feelings and being off my PKU diet. Around the age of 18 is probably when the whole PKU diet went out of the window. I wasn't taking supplements at all and was now old enough to drink alcohol which again is something me and friends would do socially and with that came late night takeaways and eating all the wrong food. Life for me around this age, and I think for any typical 18 year old was at its most chaotic and full of change. This is a time when my PKU was completely overlooked.
In the years to follow I would begin employment in catering and struggle further with long busy days being off diet and not taking supplements. The sad thing is I was mentally in a place where I couldn't see the wood for the trees. I felt like I was underachieving in everything I was doing and less capable than my peers. These feelings brought anxiety and depression as well as total social withdrawal at times. I did receive NHS treatment for Depression and Anxiety in my Mid Twenties and still wonder if this would have been needed if I was on PKU diet at the time. Or if the anxiety and depression would have not been so bad.
fast forwarding to now I am back on my PKU diet and feeling a lot better in myself. I now work full time in an admin based job role within the civil service and find that I can only fulfil my potential within this role when I am on diet. This can be a struggle day to day and I do have to batch cook meals every Sunday to keep my bloods low throughout the working week but for me its worth it as it keeps me at my best. I guess the point I am trying to make is without the skills I learnt from being a child with PKU I would have found it near enough impossible to go back on diet myself. Also as a teenager with PKU when I was off diet and levels were sky high it took me many many years to actually be able to identify the reason I was feeling as bad as I was even though it was staring me in the face. High levels are like living on the outside of life and seeing days go by but not actually feeling or remembering being a participant in them. It really is an awful way to feel and one that you can't actually understand unless you have PKU and are able to go off diet and be fortunate enough to come out the other side.
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Ordering and receiving prescriptions correctly.
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Physical and mental exhaustion.
My mother used to eat out the way of us as she felt guilty that we couldn't eat it.
Special occasions felt unfair.
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Fighting for Disability Living Allowance for us for many years and not being able to find work for herself as she was a full time carer for her 2 PKU children.
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Q12. Unable to comment.

Q13. If any further information is required from me please do not hesitate to contact me.

********** (PKU adult age 30)

Respondent 73

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I was a participant in a drug trial for Kuvan and was on it from the age of 15 to 19. Having to stop the medication was horrendous and demoralising. Having adjusted to changes while on the medication it was jarring and disorientating to have to stop it. Kuvan is a medical treatment for a condition which does not go away when you turn 18. It is logically and ethically wrong to 'dangle the carrot' of improved quality of life, then take it away.

Q3. I do not agree with NICE's view

Q4. Following a campaign by BBC Newsnight, I and other participants in the Kuvan drug trials were put back on the medication and the drug company acknowledged we should have been on it all along. Since being on it, my Phe levels have reduced and stabilised and my quality of life has improved. However, I continue to suffer from treatment-resistant generalised anxiety disorder. I have been working with a psychologist at the rare disease clinic who is exploring features of Attention Deficit Disorder die to problems with executive functioning. I strongly believe these ongoing issues are the result of damage to my brain from lifelong increased he levels.

Q5. I have experienced all these symptoms and they have all affected my quality of life. The diet is so complex, involving meal planning, cooking, and checking nutritional information, these symptoms often make it impossible to control Phe intake. The 'sugar tax' has also meant that aspartame is in so many products that is is far too easy to make a mistake, which eads to higher levels and more problems. This cycle is difficult to break without outside support.

Q6. The current support system for PKU can hardly be described as cost effective. I have protein substitutes and food on prescription, none of which are cheap for the NHS. I also have regular support from a team of clinicians and dietitians, as well as my GP. The specialist clinic also have a psychologist who I have regular support from. Aside from mental health problems, I also have osteoarthritis at the age of 31, which I am convinced has been caused by the nutritional deficit of the PKU diet. I have had to have *[no response given to this question]*-rays, physio, hand splints and GP contact for pain relief, all of which add to the cost of current treatments. The reduction in the cost of all these elements should be taken into account when considering the cost effectiveness of prescribing Kuvan for adults.

Q7. Answered as part of my last answer.

Q8. This must be taken into account. My husband and family give me constant support. My husband helps me order my prescription foods and supplements, which come in large heavy boxes. I would not be able to manage this on my own. He also helps me check ingredients, and manage recipes and cooking. I sometimes need support when going out socially due to anxiety, especially around food. I also need help getting to appointments. This takes time for my husband and family and is stressful for them.

Q9. PKU is incredibly hard to manage even if one does not have social issues like the above putting them at a disadvantage.

Q10. It is crucial that Kuvan is available to pregnant women with PKU.

Q11. I have been pregnant previously and it was incredibly difficult, and I did not have Kuvan. Cutting down protein intake to 3g a day preconception was incredibly difficult. I also suffered severe pregnancy sickness which made my Phe levels incredibly high, a risk to the baby. I had to be put on a powerful antiemetic drug. I was under an obstetrics consultant at my local hospital as well as having intense contact with the rare disease clinic. This cannot be said to be cost effective.

Q12. High Phe levels in pregnancy affect the baby, this is proven. NICE must factor this in.

Q13. Kuvan is an old treatment now, but I am testament that it works. I have the most severe form of PKU. I have only been able to slightly relax my diet on Kuvan, but this has allowed me to lower and stabilise my Phe levels. I know that others on it are almost able to follow a normal diet. It has a profound impact on quality of life, and I believe it reduces the need for prescription products and contact with clinicians and other services. This must be taken into account. The current dietary treatments offered to not get to the heart of the problem, and often their complexity makes it harder.

Respondent 74

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. This is age discrimmination. You are not helping children who will never learn to deal with a restrictive diet. Once Kuvan is removed, they will be off diet with no comprehension of getting back on diet. This is tantamount to intentional brain damage, and these recommendations seem to understand the issues of high protein. Brain development may peak early, but it continually grows.

My experiences as a 48 year old PKU are fairly horrendous. I prepare and taken supplements 5 times a day. This takes 20-30 minutes each times and causes massive health issues in themselves as my body fails to digest them.

What I do not understand is why this study is only examining BioMarin Kuvan and not the generics that have started to be produced since October 2020 when the BioMarin patentn ran out from pharmaceutical companies such as Endo in Ireland. https://www.prnewswire.co.uk/news-releases/endo-begins-shipment-of-generic-kuvan-r-tablets-and-powder-for-oral-solution-sapropterin-dihydrochloride--808600556.html

When will NICE address generic Sapropterin availability or alternative treatments such as probiotics and gene therapies. Surely the cost of a gene therapy solution is a one off and so would be more economical. Is this appraisal solely driven on a cost calculation rather than even vaguely attempting to deal with the difficulties PKU patients have through the entirety of their lives.

Q3. I do not agree with NICE's view

Q4. I was give an MRI to examine my brain development at the age of 21 but not at all since. The effects on the brain may be short term and long term and this is what the analysis of my MRI was unable to conclude. The ongoing effects on the brain of high protein is perfectly evident for all PKUs.

Q5. Daily difficulties concentration and focussing, dealing with brain fog and mood disorders is a daily occurrence. In fact, I have changde medication and regimes at least 12 times during my lifetime. During my 20s this was the most difficult and I suffered from depression and self-inflicted injury. My reliable and constant medication, Aminogran, that I'd had since childhood was discontinued. Despite moving to new medication, my whole life changed. My ability to concetrate, stay awake, learn, and perform daily tasks became so much more difficult. It was life changing. I don't want to see anyone else go through that.

Q6. The lifelong restrictive low protein diet is very difficult to maintain daily for life. Describing my health condition to employers and friends always complicates my relationship with them or my opportunities in the workplace. I am judged on the lowest common denominator of information on the internet.

I have also had difficulties as a pregnant woman with PKU.
I function best at 600-700mmol of PHE as discovered in my blood tests. However, the guidance for pregnancy recommends PHE levels should be between 100 and 300. I have tried to maintain these levels and simply CANNOT. As a result, I've had two very traumatic terminations. I tried very hard to make changes so I could see full term. But my whole life became hellish. My relationship was affected. I had depression. I could not hold my job down due to illness and inability to think straight. My relationship broke down. It was the worst event in my life and the hardest decision I ever made.

Q7. There are not many studies of how PKUs age and what support they will need as they become elderly. I was always expected to be seriously ill in my 40s from previous clinica advice I'd received. Alot of times I was told "We really don't know".

I have had servere digestive issues from PKU medication. I have had endoscopy which found nothing but also did not stop the issues which have grown worse. Exacerabated by the PKU protein supplements.

Q8. The social impact of dealing with PKU regimes and symptoms can break up families. I was very lucky in that my parents fought for me. But I was incredibly lucky. When I was told at 10 that my the latest clinical recommendation was to 'relax' my diet, my parents could see my deterioating. This video precisely explains the withdrawal and disassociation that results from high protein https://www.youtube.com/watch?v=-rs0iZW0Lb0 And it's heart breaking that the UK is still exposing it's citizens to this kind of treatment. It is barbaric that this can be sanctioned.

Q9. All circumstances vary. You will not discover this from random research papers. You must consult the PKU community and individuals.

Q10. There appears to be a disconnect between the current policy to support maternal PKu woman by providing access to Kuvan previously. Whereas this study now recommends that Maternal PKUs will no longer have access to Kuvan.

Q11. I have cats. I have been terrified to have children in the event that they have congential defects. I was advised from the age of 9, pre-puberty, that I should not get pregnant. I then did accidentally become pregnant at 28 despite being on the pill. Twice with the same partner. It was the most difficult time in my life. I do not want to see anyone else have to deal with what I went through.

Q12. Honestly the NICE recommendations are riddled with inconsistencies as if the authors are from different disciplines. It's as if the medical advice is quite clear in comprehending the difficulties of the PKU diet and the imapct that Kuvan would make. And then someone had worked their way back through the paper and stressed the economical impact of such a treatment while completely contradictory previous information. This is inadequate and unacceptable that people's lives are subject to an accounting exercise while medical advice is perfectly clear and evident.

Q13. Please consider Sapropterin generics, such as the one supplied by Endo https://www.prnewswire.co.uk/news-releases/endo-begins-shipment-of-generic-kuvan-r-tablets-and-powder-for-oral-solution-sapropterin-dihydrochloride--808600556.html We have been waiting 12 years to get Kuvan approved. While in Europe from Spain to the Ukraine are all able to treat their citizens with it. It's an embarrassment that we have no impetus to support our patients better.

If this is a decision purely based on economics, please do consider other suppliers than BioMarin. I was 31 when Kuvan was first launched by BioMarin. Now I am 48. You are affecting people's entire lives with this decision. Please respect our rights as humans and citizens that deserve our right to well being and permissble food and medications.
Thank you!

Respondent 75

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. This proposal appears both unethical and unsafe when considered more fully. Children will likely loose or not develop the skills required to continue a low phenylalanine diet, needed when the medication is withdrawn age 18 onwards and the enzyme co-factor is no longer augmenting the PKU treatment management. There is no evidence in the literature that indicates that this proposal is a safe one. There is plenty of evidence in the literature that the dietary management of the condition is challenging in adulthood. Removing the medication based on cost appears at best callous, and at worst dangerous, with the ability to cause harm, and clearly more robust evidence will need to be produced before this recommendation of withdrawing at age 18 is considered safe when considering the advised lifelong treatment of the condition.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. When considering this section, it seems that there has been very poor understanding of the lifetime nature of the condition, it remains a possibility that the committee has had a poor level medical guidance in relation to this despite evidence to the contrary in scrutinising the Committee papers. This is demonstrable in the glaringly evident contradiction that whilst the committee discussion clearly outlined that brain development does not stop until around age 25, the draft decision of not continuing the provision of the enzyme co-factor beyond age 18, based on cost, still manages to state that there was “no risk of irreversible brain damage in adults with PKU” At what point do adults become adult, is it 18 when the medication is withdrawn, is it 16 when paediatric treatment finishes, is it 25 as has been suggested by the evidence presented? The hard reality of this draft decision to withdraw a medical treatment at age 18, (that will have been been reducing blood phenylalanine levels), is likely to lead to PKU treatment failure, to be dangerous to brain health, and increased risk of phenylalanine crossing the blood brain barrier which will have an affect on continuing brain development until approximately age 25. It is truly astounding and really quite shocking that this contradiction was not checked by the committees medical advisers prior to publication, even though the committee papers clearly outline the neurological complications in adults that are found with elevated levels of phenylalanine.

Q5. I agree fully that many adults with PKU experience significant difficulties following the very restricted diet, having had experience in following this for a considerable length of time myself. Living with a condition that requires a significantly restricted protein has an impact on many aspects of my life. Every thing eaten is constantly analysed, its not possible to just have something to eat, as and when, everything has to be planned. This means thinking about the last meal whilst putting the current one together and considering the next one, to ensure the correct amount of fuel, whilst measuring and ensuring the correct protein intake. This medication has proven to reduce the burden of dietary treatment in those countries that have managed to make it available to their PKU population of responders, and crucially enable an increased quality of life. There is evidence clearly indicating this in the literature and research, as contained within the committee papers. On a personal note, living with this condition with the constant threat of neurocognitive deterioration, whilst knowing there is a treatment successfully used in many other countries that I read in the literature that could reduce this effect with lower blood phenylalanine levels and increased quality of life, which could be available but is not, is a constant source of torment. This has also increased recently with the committees bizarre and seemingly unscientific recommendations.

Q6. There is a real concern of history repeating itself here. In the 60s and 70s continuing treatment beyond early childhood was not considered necessary, however the long term effects of high phenylalanine became clear with neurocognitive deterioration providing the evidence to continue with dietary treatment. There are numerous study which detail the difficulty in maintaining dietary control in adults from all over the PKU world, and this is in those that have had dietary treatment. The draft proposal acknowledges that the medication will allow a relaxation in the diet, and this will be in childhood. Therefor the skills required to maintain strict dietary control will be at best diluted, and then suddenly age 18 these will be needed at a time of great change. Many studies detail the effects of high levels in the Committee papers, these include executive functioning difficulties, processing and working memory difficulties. These ae likely to develop as the medication is withdrawn creating a perfect storm tor treatment failure, which the draft proposal advocates. Shocking. Many of those in adulthood now experience these difficulties, please refer to the NSPKU patient voices publication which detail these clear effects on quality of life. The benefits of augmenting the dietary control have been miscalculated and ignored, which would also include benefits such as increased worth to society when these effects are reduced by tighter control in adults, never mind the significant improvement in quality of life. It seems the committee has completely missed the point as to how much the diet effects quality of life negatively. Please read the Patient Voices and widen the limited body of evidence that has been considered here.

Q7. There have been studies and literature which indicate the time that it takes to organise and deliver a strict low phenylalanine diet. This has been equated to 17 hours per week. Adults need to weave this into everyday life, career and home life. These do not have been taken into account, it’s almost as if the adults can just do the job, with no understanding of the pressures and strand. Imagine trying to implement this, start and relearn a tighter controlled diet at a time of major life upheaval of starting a new career, higher education, building relationships and then worrying about inevitably higher levels and the worry of effects on neurocognitive complication whilst the brain continues to develop. These which include executive functioning, working memory, increased anxiety will all have an enhanced effect. In my experience, with decades on treatment and continuing experience there are times of challenge through increased levels when ill, or day to day life issues which makes running the diet challenging which are not really understood by medical professionals that do not live with the diet that have provided ‘expert guidance’, dieticians have a greater insight, however the committee would do well to consider the real experts, the patients, much more closely than the NICE committee draft decision and justifications indicate when dissected.

Q8. The management of this condition by a restrictive diet has an enormous effect, not only on the individual but on other family members. Anything where food is considered there is an effect and includes meal planning, shopping needs, constraints on eating out, socialising where there maybe food, holiday choice, hospitality from family and friends. These effects would only really be truly appreciated by those that live with, or support an individual that has the condition, and may only be partially visible to the outside medical advisers, but it is most definitely experienced by those that are involved, the true experts that live with this restrictive life, day in day out. Relieving this somewhat with a medication is not only likely to improve the quality of life of those with the PKU condition, but also those that support them. Also less support will be needed in children who are provided with Kuvan, however will suddenly need additional support as they reach age 18 by those that may no longer have the skills to give that support, resulting on a potential increased burden on the health care system. Has this been costed in the modelling, it does not seem to have been? These issues do not appear to have been considered other than in passing in the decision process.

Q9. Yet again contradiction features in the the issues raised. Kuvan was first licenced for pregnant women in the UK, the committee points out that there are groups of people who face difficulties, however is unable to recommend the medication in adults equates to quality life benefits. It seems the qaly and erg considerations do not seem fit for purpose, not because of a negative decision, but that the burden of the diet and the effects on day to day life have not been captured to reflect real world experience. The costs of inevitable treatment failure when the medication when withdrawn at age 18 have not been mentioned, never mind considered in the modelling, which sems a glaring omission. There seems to be unfair treatment of adults with PKU in this consideration

Q10. This is not my area of expertise, however there is literature that addresses this in detail. There have been many lectures on this, some of which the committee’s experts may have delivered at conferences. Even a basic Google search reveals this, and Pubmed has many, nevermind the metabolic journals. It’s seems closer engagement with experts is needed here. There is evidence of successful pregnancies with the medication within the patient community as well.

Q11. Whilst I no experience of this being male, I have several female friends with PKU that really worry about this and have opted not to have children and a family because of fears of damage to an unborn because of higher phenylalanine levels because they find the diet so difficult. The comittee would be abvised to listen and take note of these stories and real world expereiences, as well as looking to the examples when Kuvan has been used to help manage the condition during pregnancy successfully. The literature clearly outlines this, as indicated in the Committee papers.

Q12. This is astounding, shocking, surely verging on dangerous. There is plenty of literature, clinical evidence and real world experience of this that others will have provided

Q13. The draft recommendation and supporting evidence appears to be disjointed and in places contradictory. It appears that some evidence has been ignored, both in the committee notes and particularly from countries where the medication has been routinely provided for years. It is welcomed that the medication is being considered for children, but the justification to withdraw at age 18 appears chaotic, not based on evidence, in real world experience and has the very real potential to cause treatment failure in young adults, despite the evidence in the committee notes, and this is shocking. It is really not clear how this evidence was not taken into account. In my own practice NICE opinion and guidance is regularly referred to and quoted, as a beacon of excellence. However in scrutinising the draft recommendation and supporting evidence, there is a feeling of shock, not at the negative decision as such, but with the contradictions and disregard of the evidence, both literature and real world from those living with this restrictive lifelong condition.

"Sapropterin allows patients to manage their conditions more easily, reduces symptoms, and provides peace of mind about blood phenylalanine levels. Meindert Boysen, deputy chief executive and director of the centre for Health Technology Assessment at NICE

Respondent 76

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. No human being will cope with having a life changing drug allowing a normal life to be then taken away. This will impact not only metabolic state but mental health issues costing the NHS far more than giving the drug for all pku patients for life!

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. Quality of life is very dependent on phe levels. It is difficult enough sticking to a very strict diet without complications of brain fog, low mood and irritability. This affects not only yourself but other family members who are closest to you which is very difficult.

Q6. Absolutely I am in my forties and worry now what my future might hold for both me and my family because nobody actually knows. This means not only a very restricted life but also no idea of what is to come. In terms of life experiences I do believe I could of done better at school or in my career if I had the opportunity of a treatment such as kuvan. No matter how good you are at the diet it is proven not perfect meaning all the effort you go to day in day out can be affected by a simple cold or infection.

Q7. *[no response given to this question]*

Q8. The affect this had on my family growing up is massive. I owe my life to my mum for helping me stick to a diet that is in humane along with dietary prescriptions necessary for the management. Even these are not available on the NHS like diabetics have. We all have to get a prepaid prescription...we are the forgotten illness that nobody knows about.

Q9. Absolutely not. I have two luckily healthy children without PKU. This was not achieved without hard work and dedication from myself and family. I couldn't enjoy my pregnancies due to such huge restrictions and found it very difficult at times. I would like more children but due to having PKU and the unavailability of Kuvan I have decided not to go through another pregnancy ever.

Q10. Kuvan should be available to all including pregnant women.

Q11. Planning to have a child is massive and even harder when faced with the potential risks for a PKU adult. Once you have conceived there is no going back and all you want is for a healthy baby. The pressure on the mother is extremely high because this is not just for yourself but your husband. During my pregnancy I struggled with keeping weight on and energy levels due to being on such a small amount of protein. I have had two children but would not do it again so PKU has restricted my, if it weren't for my diet I would potentially of had a third child.

Q12. What can you say - they have no idea. If it were their child it would be different.

Q13. I think it is disgusting to even consider what has been recommended. PKU is PKU NO MATTER WHAT AGE YOU ARE. We have put up with this same old treatment if you can call it that for a long time. It's time we moved forward with the rest of the world!

Respondent 77

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I dont think Kuvan should be taken away from anyone at any age. I think it is stupid because people at aged 18 are not yet ready to manage their diet, whilst they still have their education to deal with, their work to deal with, their family and relationships to deal with. Limiting the potential of what the person can reach leading a life and taking that away from them is a cruel thing to do. Turning into an adult doesn't make life it easier, it makes it harder and taking away a medication that makes life that little bit easier at 18, or any age, is cruel and unbelievable.

Q3. I do not agree with NICE's view

Q4. After suddenly losing my mother to cancer, whilst on a extremely restrictive and difficult pre-conception diet as a newly-wed young woman, my dieticians advised me to come off diet due to the trauma and grief I was going through, as it would be extremely difficult to follow such a complex and time consuming diet and still function. Due to the effects of coming off diet and the depression and anxiety attacks and blur that then ensued, it led to my marriage failing. The results of which are not reversible.....Nothing can ever make up for that.

In terms of my day to day life and my work life, I sometimes have no energy, lack ability to focus and this holds me up in my career - see below

Q5. I get massively lethargic, sometimes to the point of being bed-bound - I cant move. I can't go to work. I can't hold a conversation because my brain cant bring out the words I want to say. My brain cant process information quick enough for me to maintain a normal conversation. It goes straight over my head. I then feel self-conscious and it affects my self-confidence and self-esteem and I just have to remove myself from the situation. So this affects my social life and ability to socialise normally and my work-life.

With regards to headaches, I get a very very distinctive headache to the point where I can tell a PKU headache from a normal headache. It is a very distinctive type of pain which again affects my focus - another reason why I know it is a PKU headache. When it is a PKU headache - nothing in the world will take it away - nothing works, no tablet, no drinking water, no dark room , none of the usual remedies work.

Q6. After being on the pre-con diet and the fact that it failed, and the fact that my marriage broke down so soon after getting married and trying for a baby, it has made me dread the thought of ever having children, even though it is the one thing I want most in life.

When going through traumatic times throughout my life, it has been nearly impossible to maintain my PHE levels which has also resulted in depression and anxiety of some sort; those are the memories that I feel and that I have to live with and that I fear of happening every time a traumatic ordeal happens in my life. and sometimes its not even an event that is that traumatic, but not being able to manage PHE levels makes any situation a million times worse. For example, I have to live with the memory that I have self-harmed in the past so yes, the effects of past high PHE levels does affect my future and my life experiences. Any future relationship I have will have to accept the damage of my past.

Q7. I'm currently on waiting list for adult mental health care services for depression and anxiety . The waiting lists are very long and I cannot afford to pay for private therapy . I have tried it, but I cannot manage my household bills, rent , car etc. It is impossible and I haven't applied for PIP because of how difficult I have seen that it is to get it for PKU patients and the additional stress it would put me under to get it. I've seen others apply for it and it is seems like a traumatic experience and I don't want to go through that.

Q8. Recently losing my mum, who taught me how to manage my diet and would always find new things for me to be able to eat, and helped me with my cooking, has had a massive impact on the management of my diet. My mum always was the one who helped me with my diet , even as an adult.

My former husband always tried his best to understand and help me find foods that I was able to eat however there were many , many times where it caused a very big strain on our relationship , especially when we went to eat with his friends and family, as they could not head around it, through no fault of their own.

Other than that, I have absolutely no family support , i.e. I am totally unsupported because the members of my family, including my dad and brother, to this day, do not understand how to manage this diet and that is not lie. This can cause some friction and pain on my part.

Q9. No, I don't. They are not treating people fairly because all the people mentioned above, (which includes myself obviously as a woman who would like children in the future), would , if offered the chance to take Kuvan, be able to live a normal life without the stress and strain of having to count the amount of protein they have a day and weigh it out and be able to socialise in restaurants, women would not have to struggle to have children or make up stories that they cant have children to hide the fact that they won't have children because they dread the process, never mind the fact that 90%of women with PKU who have had babies are unable to manage the diet for themselves when taking care of their newborn.

Please tell me how that can be justified as fair?

Q10. What NICE need to take into consideration is that before even women can even consider conceiving, they have to go on a ridiculously restricted low protein diet which includes counting and weighing food with extreme minimal exchanges, and once they have conceived, the women have to send in two blood spot forms a week for their levels to be monitored which can fluctuate massively throughout pregnancy, just to ensure their baby's growth is healthy (I was told between 0g and 60g of protein a day depending on my blood PHE levels and the baby's needs). Blood test results might take days to get results back and results may be days out of date so adaptions to exchanges and diet is actually a bit hit and miss. This, for the PKU community is no joke and affects every single women who has the condition, including myself. The consequences of not following the levels that we would need to be at are literally tragic and it is actually sad that they would not take that into consideration.

Q11. After attempting the pre-conception diet for the first time, and with it being a traumatic experience and adding so much strain to my marriage that it contributed to the breakdown of it, I wouldn't even know where to start with pregnancy going forward, The one thing I want most in life is children but there are all these worries. The pre-con diet causes stress and stress restricts you from conceiving; yet, having an unplanned pregnancy will lead to a handicapped child. Even if it is planned, you may be incapable of managing your levels throughout the entirety of pregnancy, and the child might still end up handicapped. This is a heartbreaking and terrifying thought for me which is making me reluctant to have the one thing I have always wanted. Never mind the thought of having to try to manage the diet whilst taking care of your newborn. That sounds like an impossible ordeal for me and I am sure I am not the only PKU women to say that.

Q12. see above

Q13. NICE says the brain damage to adults is reversible by dietary therapy, but even if it were possible to resume and adhere to dietary therapy, the damage that the brain damage and mental health issues have caused up to that point in a person's life and relationships is not reversible. You can't get back a failed education or a failed marriage.....

I find it disturbing that I was given the choice at 11 years old, without my parents influence, to give up the diet which in practice, affected my education my massively, but being a child , I didn't know any different and just wanted to eat normal food like all my friends. this was in the 1990's (I am 33 years old now!). I should never have been offered the choice to stop treatment.

I also find it disturbing that I was given the choice by my dieticians as an adult to stop the PKU diet when I was going through the trauma of the

loss of my mother and the breakdown of my marriage because they recognised that it would be too difficult to follow such a complicated regime under such circumstances.

I have taken the decision not to ever, ever go back on a pre-con diet and, if the time came, would prefer to have an unplanned pregnancy because the stress and strain of a pre-con diet is not conducive to a healthy life style or a healthy relationship and would no doubt ruin my chances of conceiving because of stress. The fact that you have to wait 6 months to get your levels right, is just too much too bear and I can't see how that makes conception something natural or an enjoyable experience, like it should be. For most people, planning for children is an exciting time, but for women with PKU, we dread it.

The way I explain myself to people who are unaware of the diet is that I am vegetarian, gluten free, vegan, dairy free, no fish or nuts or pulses all in one person! Which then confuses the people I speak to that unaware of the condition! In terms of quality of life, maintaining a social life is also very difficult and we are unable to have meals in restaurants or anywhere other than our own homes because we cant risk our PHE levels being incorrect. It is impossible to expect any one to understand - it's too difficult - it takes years to understand it.

Changing GPs in a nightmare - you need to explain everything all over again. Sometimes they are reluctant to prescribe the products as they consider them to be luxury or not prescribe enough products and leave me short. Once, I was not even prescribed my supplements, which left me bedbound for days, with no energy, until I received emergency supplies.

Respondent 78

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I believe this is cruel at best! This is when adolescents are becoming young adults, going on to further education or joining the workforce. To have led a relatively ‘normal’ life food wise and then just as they are branching out and becoming more independent they will have to go back on a low protein diet. This is detrimental to their mental health. Managing and maintaining the diet takes a lot of time and organisation. This ruling will have an adverse effect on these young people’s lives. This diet has a huge impact on people’s lives and they often feel like outcasts in social settings.

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. My children have Classic PKU and keep their levels at a fairly good range. Both have problems with only slightly elevated levels. They struggle with concentration, tearful, low mood, forgetfulness, tiredness and irritability. My daughter often has 3 naps a day when her levels are only just outside the range. I believe she would be unable to hold down a job if she came off diet as we know how much she struggles when her levels are elevated by just 100.

Q6. Mental health problems play a huge part in people who come off diet. I know a few adults that have come off diet due to being told to by their metabolic clinics, they have constantly struggled with day to day life and after returning to a low phe diet they have managed to turn their lives round. One in particular was a straight A student while on diet, he was told to come off diet and that it wouldn’t affect him. He went to university and had to leave after the first term as he couldn’t make the grades. He went back on diet and went back to university sadly not able to join his original group of friends as his levels and concentration needed to get back to the level required for him to continue with his education. He passed with a 1st. Coming off diet had a huge affect on him trailing behind his peers, his words! He also kept failing his driving test due to concentration once back on diet and with good levels he passed.

Q7. Living with a severely restricted diet has a massive effect on the individual’s mental health. My daughter is going through her second bout of anorexia, the first a couple of years ago. She has just put some weight on and has now reached 6 stone. My heart breaks watching this. I know we are fortunate and the 2 teams involved with her care work well together. My daughter has a FaceTime call each week to stand on the scales and to say what her next step to recovery is, how many calories and how much exercise she’s allowed, it was no exercise but now she’s reached 6 stone she is allowed 20 minutes a day. Her life is totally obsessed with food and the amount of phe she can take. She is constantly on anti depressants and now on medication to help her sleep. When her anorexia is better she will be returning for the fourth time to cognitive therapy to help her deal with the diet in a healthier way. It has been suggested in the past that she comes off diet, my daughters reaction as she does want a family in the future is that it would be like giving a blind man sight and then taking it away from him! Eating disorders are sadly common with PKU. This has a massive effect on all the family. My son often gets in a low mood over being socially excluded when it comes to dining out. He is 6’2” a grown man and is only able to have 135g of chips a side salad and depending what they are a side order of seasonal vegetables, definitely not peas as they are too high in phe! Also when the ingredients changes in his favourite foods or is favourite low phe foods are taken off prescription. He is 8 yrs younger than his sister, she is his hero, I pray he doesn’t follow her very sad & hard path.

Q8. I have had 3 children with PKU, one very sadly died when he was 6. I have one child without PKU. Helping to manage their land maintain their levels still has a huge effect on us as a family. My adult children have classic PKU so heavily rely on low protein prescription drugs, as there is a 2 week turnaround on the ordering of these foods, I need to be one step ahead, I can’t pop down the shop if we run out. My son is now a grown young man but not able to organise his stocks and deliveries, he needs reminders and encouragement to take his bloods. I am in the process of getting him to take more control over his independence with the diet. He works out his exchanges and cooks himself dinner a couple of times a week. Ordering his own supplements and food for the month isn’t high on a 19 yr olds list of things he wants to do. I feel I don’t want his PKU to be a chore. With my daughter struggling with PKU and anorexia it is heartbreaking supporting her with her constant struggle with food, supplements and mood swings, we try to avoid the kitchen when she is preparing food as we have all fallen foul to her behaviour at these stressful times.

Q9. My first born who has sadly died had severe brain damage and PKU , his brain damage was due to being starved of oxygen at birth. He would of been in the same group as my other 2 , I didn’t discriminate between them. Equality in my experience is to include all. Not everyone will be a responder but could be tested at not a great expense. For those that responded it would have a huge positive effect on their lives as has been proven in trials and worldwide. I work on a cardiac ward we treat everyone that comes through the door, travellers, homeless, disabled, diabetic, poor, rich, cashiers, professors, bus drivers, tv stars, Lady’s, Lords, domestics, doctors, nurses, we use translators when needed, we don’t discriminate they need our help and we give it. I am a strong believer in quality of life, this drug would give a good quality of life to those that respond. I do question the equality and discrimination of giving this drug to children and then discriminating them when they reach 18.

Q10. I am totally shocked that the committee were not aware of the risk with Maternal PKU, we had a clinic with very limited knowledge of PKU, we weren't offered a metabolic clinic for 10 years and then only when I found out they existed! Our consultant had one other PKU patient 20 years prior and even he knew that my daughter would need to be on a stricter diet before conceiving and her bloods would need to be within a very narrow range to have a healthy baby. This drug would help assist them with better management during this very stressful time, ensuring a better quality of life.

Q11. My daughter has a constant struggle with food and the diet she is of child bearing age and hopefully in the next four years she will have a successful pregnancy. Kuvan would make a huge difference to what we already know is going to be a difficult and stressful time and helping with her blood levels to prevent harm to the unborn baby. Her levels will need to be maintained as she becomes a mum to give her baby and herself the life that others take for granted.

Q12. The effects on a baby born to an uncontrolled PKU mum is well documented for neurological damage that is done. As my daughter has classic PKU and a low phe tolerance we have been told her baby would have brain damage if she accidentally got pregnant. Having had a severely disabled son myself I know the cost of his supportive care. His hospital admissions were regular, 2 weeks out 4 for the first 2 years. Doctors home visits twice a month, paediatric district nurse twice a week, health visitor once a month, more if needed. Consultant visits monthly, Speech and language, weekly, physio weekly, jejuneostmy changed fortnightly with the need of a consultant, radiographer, radiology assistant, nurse, porters plus the ward based nursing team pre and post procedure. His respite care was a qualified nurse one night a fortnight that stayed awake to watch over him. He wasn't allowed respite care from anyone unqualified, we later became respite care and know the cost implications of that. When he managed to go to school he had one to one for all the school day. We were very lucky with the care my son received, we know of the great cost that came with this. I realise my sons disability was extreme but it does highlight the costs in all aspects of caring for a child with a disability. This was before his disability benefit, my carers benefit and mobility benefit. Council tax discount .

Q13. On giving this medication to under 18's you are discriminating on age as the brain hasn't stopped developing at that age. Equality to offer a better quality of life to those who respond. Helping with mental health , acceptance and social inclusion. A better quality of life!

Respondent 79

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Put yourself in the shoes of a child, who is given the luxury to eat and drink the same as children around them, to then be told on their 18th birthday, that now they have reached adulthood, they are going to have majority of foods they are used to taken away if they want to remain healthy. No more meat, cheese, eggs, milk, beans, bread, pizza, etc. any other high protein foods.

Anything that does have phe in (even as simple as potatoes, chips and cereals), that isn't prescription products now need to be hugely limited and weighed out to fit in with your new daily allowance of less than 10g protein a day.

Oh and by the way you also need to now increase your protein formula / medicine (whether you like the taste or not) to make up for no longer having access to kuvan...

….and this is for the rest of your life!

Speaking from experience of living on life long restricted PKU diet, if I was offered Kuvan as a child / teenager, it would sound appealing at the time, however there is no way I would be able to return to a strict PKU diet once Kuvan is removed, after 18 years of not 'learning the diet'.

I truly feel that this is going to lead to many more health consequences in the long run when new adults choose not to follow restricted diet after having a medication they have grown up with removed.

Therefore potentially costing the NHS more work and money in the long run trying to encourage and support adults who are either struggle to follow diet after having kuvan medication removed, or dealing with the various health consequences. Then there is the impact of maternal PKU.

As a mum who has to follow a very strict PKU diet as well as very restrictive pre-conception and pregnancy diet to avoid devastating health consequences for my child, I know how difficult this is and that is with growing up on and continuing to follow life long diet I am already familiar with.

Q3. NICE's statements are contradictory

Q4. Diagnosed depression and anxiety which is noticeably exacerbated when phe levels aren't under control.

Experience huge impact in mood, decision making, self esteem - all affects every day life and working life.

Q5. From experience, the way I feel and in correlation to regular phe blood monitoring, 'brain fog', forgetfulness, tiredness, confusion, low mood and feelings of irritability is certainly noticeable with high and unstable phe levels.

Optimising the quality of life for adults is equally as important as for children and teenagers. We need to be mentally and physically healthy to manage diet, everyday life, contribute to society, and manage work, life responsibilities and dependence. This all becomes very challenging when phe levels aren't under control.

Q6. Uncontrolled, unstable and high phe levels leads to noticable long term affects. Not only chemically in the brain but mentally and socially. I often struggle with the mental impact of regretting times in my life where I have relaxed diet (although only slightly, but has it still impacted phe levels). - This led to me becoming unable to focus, learn and stay motivated, which in the past has led to failed exams, poor performance during study and work.
Ultimately resulting in not being able to pursue the career I had initially dreamed of, and taking longer to achieve goals.

The mental impact of feeling like you have 'failed' yourself or underachieved, all because of not keeping phe levels under control is huge, and leads to a constant battle of self-blame, self-criticism and low self-esteem. This in turn affects mental health, confidence, social and life

experiences.
I know from talking to other PKU patients, this is very familiar to them also.

Q7. Throughout my life I have struggled with mental health issues in which some are directly and some indirectly related to PKU. I know many other PKU patients who have experienced very similar experiences.

I believe, the effects of being bullied at school for my PKU, phases of being made to feel ashamed of it, the everyday challenges of maintaining restricted diet combined with PKU symptoms of fluctuating phe levels, all contribute to these effects.

I also struggled tremendously following the birth of my son. At which point my phe levels were pretty much double where they were during pregnancy. I feel this was due to not only the challenges that come with being a first time new mum, hormones, postnatal blues etc but combined with trying to manage and adjust to returning to a restricted PKU diet after having a higher tolerance towards the end of pregnancy and deal with high phe levels.

Adjusting post-pregnancy, from 20 exchanges to 7 was challenging after only 3rd trimester at higher exchange tolerance. It would be a lot harder to achieve this adjustment after 18 years of growing up on higher tolerance, to then reduce exchanges once Kuvan is removed.

I still experience mental health symptoms and think I always will, also currently having investigations relating to gut symptoms. This leads to more reliance on healthcare to help manage my symptoms, as with others who experience effects of PKU.

Q8. *[no response given to this question]*

Q9. *[no response given to this question]*

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. Kuvan should be an available option to ALL those who respond and would benefit from it. No matter their age, background or what stage of their life they are at.

The idea of allowing access to this treatment up to the age of 18 years old will likely cause more implications for PKU adults. I truly believe, from someone who lives with PKU daily and been through pregnancy, that it would be so difficult and even more mentally challenging to restrict dietary intake and increase supplements after removing a modern treatment that has so many benefits over the ‘old’ dietary treatment.

I really fear for how this age restriction will affect children and their families. It will lead to less adherence to diet as an adult, resulting in more physical and mental implications with added pressure on the health care practitioners and the NHS as well as higher risks of maternal PKU.

Please improve the lives of all those who would benefit from Kuvan and the lives of future generations without a limit to age restriction.

Please closely consider ALL comments from the PKU community.
We all know first-hand the challenges of restrictive diet, life-long PKU challenges and the challenges limited access for this modern treatment based on age restriction would have, incl the mental impact as well as added pressures on the health care practitioners and NHS.

PKU doesn’t go away once we turn 18! It is with us and our families for LIFE, and therefore surely it is only fair to all have equal access to treatment options throughout life!

Respondent 80

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. To grow up with this condition whilst being on the Kuvan .. only for it to be no longer available to you because you have reached the age of 18..! Where is the sense in that decision??

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. I have watched my grandson experiencing mental health problems .. depression anxiety..

Q5. All the symptoms listed above

Q6. *[no response given to this question]*

Q7. *[no response given to this question]*

Q8. Definitely yes... especially if you might be the only child/ young adult in that family with the condition.. it sets you apart and makes you feel isolated

Q9. I do not believe Nice has considered testing people fairly at all

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 81

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. As you have said yourselves the transition from adolescence to adulthood is challenging for people with PKU, why would you add the extra pressure of taking away the drug they have relied on. It seems barbaric that this would be a time to introduce an extremely difficult and time consuming diet. This will have an effect on their mental health at the very least. From firsthand I know how socially excluded some people with PKU feel.

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. From the adults I know you can tell when their phe levels are raised. Most noticeably, tiredness, irritability and low mood.

Q6. As it has an effect on the PKU adults I know I would say it it's very necessary to consider the long term effects.

Q7. One PKU adult I know has extra costs within the NHS for an eating disorder that has been put down to PKU and therapy for her PKU. These amount to twice weekly appointments with different hospitals. One other PKU adult needed anger management for 6 months, this was due to his anger of being on an extremely restricted diet.

Q8. I am friends with a mum of 2 adults with PKU, it has a huge effect on her daily life. Shopping at 5 different supermarkets as you can't get all the products from one place. Cooking 3 different meals as the 2 with PKU have different tolerances to phe. Baking bread 3 times a week, the guilt for not baking more while holding down a full time job. Making sure the prescription food and supplements are sorted and 'nagging' for blood tests to be done. Continuous worry about their mental health and trying to make sure they are included with social events. Eating out is always trying and often needs to be preplanned and food taken.

Q9. Offering treatment to everyone is equality.

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 82

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Pku is a life long condition not a childhood condition, the effect of high phe level on an adults brain is detrimental.

Q3. NICE's statements are contradictory

Q4. High phe levels have a highly negative impact on my mothers mental and physical well-being. She finds many "normal" tasks highly challenging and unable to do due to this. And the effects of a spell of high phe levels can have long lasting effects

Q5. High phe levels result in my mother being unable to do most things, preparing her meals, driving, having the capability to make day to day decisions

Q6. High phe levels have a detrimental impact on the brain which of course will have a long lasting effect therefore it is an effect on their future health and what they can do in life

Q7. My mother has to pay for prescription foods to be able to eat, over the years she would have spent thousands on this alone. Luckily in today's age there are more shop available items that can be eaten however as a "health food" item they are more expensive. As well as the large cost for lots of fruit and veg which make up the key things that an individual with pku can actually eat.

Q8. *[no response given to this question]*

Q9. *[no response given to this question]*

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 83

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. This would be detrimental to the young adults health as the child will miss out on sl much learning about PKU up until the age of 18 and will not know how to implement the diet at 18 after having so many diet restrictions lifted from taking kuvan

Q3. I do not agree with NICE's view

Q4. Evidence has shown that the brain is continually developing and maintaining without kuban or strict diet individuals with Pku will suffer long term brAin damage

Q5. High phe levels makes dau to day living extremely difficult and basic tasks do not always get completed when the is high

Q6. High phe levels are detrimental to a person with pku health and well being

Q7. THE PKU DIET SEVERELY RETRICTS OUR ABILITY TO LIVE I HAVE EXPERIENCED DEPRESSION ANXIETY AND CONTINUOUS STOMACH PROBLEMX AS WELL AS DIFFICULTS WITH SIGHT AND HEADACHES

Q8. PKU SEVERLY IMPACTX FAMILY MEMEBERS IT IS ANOTHER LANGUAGE TO LEARN RESTRICTS WHAT WE EAT AND DO FREQUENT APPOINTMENTS and calls with health professionals

Q9. I consider this as further discrimination as these people with additional needs can not and maybe do not have people to advocate for them

Q10. It is extremely difficult and restrictive to to maintain the pku diet when pregnant and this does present additional risk to the unborn child

Q11. It is extremely difficult and restrictive to to maintain the pku diet when pregnant and this does present additional risk to the unborn child

Q12. Again this will cost the NHS more in terms of care needs to support the child with additional needs as a result of pku

Q13. As a mum of 3 kids with pku it is extremely worrying that my kids would be given a drug that would give them so much freedom and lift all of the restrictions around their diet for it to be removed at the age of 18 when they would be considered as adults but would not be aware of how to implement the pku diet and how if not implemented it would negatively affect them. Also it is hard enough to try and follow the pku diet as someone who is willing to do so

Respondent 84

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I feel this is wrong and very unfair. The transition from adolescence to adulthood, is a very challenging time, this is bound to affect their mental health.

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. My grandchildren both suffer with low moods & lack of concentration when their levels are too high or low. One in particular suffers badly from tiredness, working and sleeping, not able to socialise or join in family events at these times. She also suffers from irritability.

Q6. *[no response given to this question]*

Q7. Both my grandchildren have had to have counselling because of their PKU, one because she was made a social outcast by teachers at school. One has been having therapy’s for several years to help overcome the mental problems that stem from PKU.

Q8. The stress can be a real factor in families breaking up. My daughter needed our support to take her and her child to the clinic which was 100 miles away after her husband left. We have watched her carry the burden of the diet and supporting her children with the emotional side of having this difficult condition for the last decade. I strongly believe it has affected my non PKU grandson greatly.

Q9. *[no response given to this question]*

Q10. We were advised many years ago that if my grand daughter became pregnant while her levels weren’t in range that the baby would have neurological damage. Knowing from my time as a nurse that the cost implications of looking after a child/adult with neurological damage is high.

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 85

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Speaking as someone who was removed from diet by consultants at a GOSH in 1979 at the age of 8 (which was norma at this time), I am fully aware of the damage this does. I needed to go back on to diet for a variety of reasons in the early 90"s (age 21) for example mental health issues- Depression, anxiety, bipolar behaviour, brain fog, social anxiety etc, however at this point this need came to a head as i found myself pregnant and struggled to cope with the introduction back to the strict low protein diet as a matter of urgency at that time. As a result of my mental health and confusion and the conflicting advice of others, i reluctantly went through a termination of this pregnancy. THIS COULD OF BEEN AVOIDED COMPLETELY HAD I BEEN UNDER TREATMENT - PKU DIET. Additionally I found at this time that the Treatment - PKU diet was being RECOMMENDED FOR LIFE DUE TO THE NEGATIVE EFFECTS ON PEOPLES LIVES. I have from this time been struggling to cope with the reintroduction to the strict change in lifestyle required for this diet to be implemented well, and the changes to advice and foods available and how to access them, and a constant feeling of hunger which I experience on PKU diet when I was a child too. (Another difficulty of PKU) Subsequently this has led to more physical and mental health challenges for me on going from this time.

NB I am aware that the removal from diet at 8 Years old did some damage to the neurological make up of my brain and would have further

made return to diet difficult due to cognitive and executive functioning difficulties as well as my depression and anxiety conditions at this time. This will be similar to experiences of many PKU adults my age.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. To be plain I have struggled to maintain the PKU diet (See section 1) and so have had many occasions where I am aware of high levels of Phe in my blood. Over the past 27 years I have struggled to cope with life in general even the most mundane of tasks become overwhelming to the point where I have not had a full-time job for 27 years, I am unable to cope with the organising of a job, my diet and my family responsibilities, and even without the added stress of working outside the home whilst being on diet i still have many days where I cannot function how others seem to with ease. I cannot organise my thoughts or tasks, I go off point a lot and get in to a mess. I have real difficulty in advocating for my self to the point i don't speak of my needs to others I cannot find the words in the moment to express myself and can be talking about something and then forget what i am talking about whist i am talking about it and appear ridiculous. I quite literally at times become mute. This puts me a a complete disadvantage to most people I would say. without even mentioning the difficulties of maintaining the PKU diet during a work day.

Q5. I have experienced from an early age and continue to have brain fog, Extreme tiredness, attention difficulties, sleep issues, mood swings, social isolation, social anxiety depression, OCD tendencies, clumsiness , memory issues- trouble with taking in and understanding information, suicidal feelings, bad decision making. I was diagnosed as having severe clinical depression in 1998 and this has been a theme through out my life. The medication or supplements i have to take daily for my PKU has been and continues to cause digestive issues acid reflux, IBS, and gallstones. Although it has improved over the years in taste and smell it has in the past caused a nasty lingering smell on my breath which is difficult to get rid of and has been awful to drink because of texture and taste that can make one physically sick./vomit.
Social events and work socials are not wonderful as they almost all revolve around food and this is a real issue for a PKU adult as well as children, the difficulty in accessing out side of our own kitchens and especially in restaurant, pubs, take aways etc, any foods that can be eaten safely is extreme and often impossible. This probably is one reason why a lot of teens will stray off diet too. Even if it were for just 'drinks' this is a problem too for me because of the problem of hidden aspartame in any drinks which is high in Phenylalanine. and leads to intake of damaging phe without my knowledge. This all exacerbates any social anxiety i already have and most often I decline the social event. It is extremely difficult to monitor my levels as blood tests need to be sent away and I have to wait for results that can take any thing from 3 days to weeks for results and I have had many times where never received a result at all.
I have noticed as I have got older especially in my 40's i started to experience different pains and numbing in hands, feet and prickly sensations around my body and was told i had Fibromyalgia and now as a woman going through menopause I have extra difficulty controlling my PHE levels, despite me not having so many young children requiring help i have more and worsening symptoms than when i was younger. The menopause has made it extremely difficult to cope at all at times recently and now I have severe eczema over my body too as well as extra weight i never had before. This has made exercise difficult although this has always been a chore as I get so tired during and after the all fitness exercise.

Q6. I DO NOT AGREE (SEE ABOVE) Having high PHE levels has contributed to continued mental health and cognitive issues leading to lack of opportunities in education, career and have become a large factor in my economic status and quality of life experience in the past, now and for my future and old age. Which causes continued stress and anxiety for me being aware of the effects of PKU seeming to become more difficult as i have got older and harder to keep control with every effort of my PHE levels.

Q7. SEE ALL ABOVE SECTIONS 1-3 - and factor in all the health problems associated with these, from now into my old age including what if i cannot look after myself and need somebody else not familiar with living or providing care for PKU including the continued deterioration of my PHE control and effects on mental and cognitive/executive function as well as the well know low bone density seen in PKU patients especially women because of lack of nutrients and and access to diet for maintaining bone health.

Q8. Family Members Mums, Dads, Partners, and children are directly affected by the PKU, they have the financially burden the stress and anxiety and have to cope with the PKU Adults behaviours and meltdowns, upsets along their personal journey as well as coping with their own life. It take toll time together on Family holidays, days out and restricts these normal everyday practices, making them limited strained taking away from the relationships developed within the family dynamics.

Q9. Not all considerations have been taken in to account but to be fair i have not had a place to raise these issues before other than with other PKU adults on social media so having the problems heard from PKU adults would be difficult given this. This does take away from the fact WE SHOULD BE ABLE TO HAVE A PLACE AND TIME TO TALK ABOUT THE EFFECTS ON US WITHOUT JUDGEMENT AND DISMISSAL, OF OUR NEEDS AND LIFE EXPERIENCES AS PKU ADULTS WITH A WAVE OF THE HAND. MORE NEEDS TO BE DONE FOR THIS. There is also a generational difference in how PKU effects the individuals it seems as treatment with PKU diet was better through time, however many adults removed from diet have seen many effects of High PHE and this also has impacted their ability to maintain the PKU diet for long periods of time A national register would be helpful toward gathering more data for studies with this in mind.

Q10. Although i personally was able to get through most of my pregnancies pretty well upon giving birth the effect of the sudden and extreme high PHE levels felt (which is well known to be the the case in all PKU women) I suffered awful postnatal depression anxiety and inability to cope including to feed myself adequately out of control, including a persecution complex, unbelievable tiredness brain fog and complete breakdowns wantig to end my life. Thisall started within hours of the births. Kuvan would eliminate most or any of these issues.

Q11. Unplanned pregnancies would have entirely better outcomes, and younger women would consider having families where now some are now starting to take extreme measures as to
ensure they never have a family because of the difficulties of pregnancy, and after effects of the high PHE upon birth as i described above, but also the difficulties of having a family and maintaining the PKU lifestyle needed to be well controlled.

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 86

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Should not be stopped for 18 year old as it should be avaible to everyone with PKU irrelevant of age, this is age discrimination. IHaving a relaxed diet then have to go back to a restricted diet will be hard to carry out

Q3. I struggle to keep my levels down on a day to day basis as the restricted diet means i would go hungry. Therefore my raised levels of Phe do impact on my mood which has lead to me suffer with depression

Q4. I am on anti depressants due to my high levels of Phe affecting my mental health.

Q5. I can relate to the above symptoms as I experience some of them on a daily basis, Eg brain fog, tiredness and low mood

Q6. I believe my quality of life would be improved if I was able to have access to Kuvan, as I would like to be able to get my high Phe levels down so that I feel better.

I would like to be able to eat out with friends without feeling anxious as this then leads me to avoiding socialising with friends when I know food is involved

Q7. Depression is the main health issue that I currently suffer with which can sometimes stop me from going into work or being sent home. I also suffer with eczema which is linked to my PKU

Q8. I rely on my mother to help me on a day to day basis with my prescriptions and shopping. I try to see to my diet myself but by the time I get home from work I am so tired that I would not be able to start making bread, cakes etc therefore my mother helps out when she can

Q9. Everyone with PKU is part of a disadvantage group by not being allowed full access to food which is a necessity to avoid going hungry and to maintain proper health and wellbeing

Q10. KUVAN should be given to women like me (I am 24 years old) prior to conception. If this was not available I will have to reconsider about having a family of my own

Q11. This statement from NICE contradicts the previous statement. The evidence that Nice have based their decision on not to give Kuvan to adults is based on evidence from other countries and I have read of women with PKU in America given birth to children with disabilities, therefore, this should be taken into consideration

Q12. KUVAN should definitely be given to women with PKU in order to avoid birth defects (I am finding this extremely difficult to write about as I would like a family of my own)

Q13. Kuvan should be made available to all people with PKU irrespective of age, disadvantage group or weight.

I was very upset to learn that one of the deciding factors for under 18 year olds being approved to have access to Kuvan was weight. I have lead a restricted diet all my life going hungry at times which has lead to my Phe levels rising and I am now unable to get them back down without going hungry. I do not consider myself overweight but I need Kuvan to get my level back under control so that going forward I can improve my mental health and look forward to the future.

Respondent 87

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Should not be stopped for 18 year old as it should be avaible to everyone with PKU irrelevant of age, this is age discrimination. IHaving a relaxed diet then have to go back to a restricted diet will be hard to carry out

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Respondent 88

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I believe your proposal to take Kuvan off of children when they reach 18 is extremely unfair. I have spent my whole life on this extremely restrictive diet and i still find it hard to follow. I do believe that to give a child Kuvan and then expect them to learn and follow such a restricted diet from the age of 18 is not only cruel but would also be detrimental to the person with PKU's mental health and well being. In your proposal you have said that the transition to adulthood is a challenging period with PKU patients, I feel like your proposal to take Kuvan off a patient at this time would be a mental health crisis waiting to happen. As a teenager I really struggled to manage my dietary treatment on my own and this was after growing up on this restricted treatment, I can only imagine how much more difficult it would have been if I had no experience of such a extremely restrictive treatment.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. I feel that NICE hasn't't taken into account the affect PKU has on an adults quality of life. High Phe levels have a big impact on my quality of life as I struggle with feelings of irritability and increased symptoms of depression and anxiety. I find that due to the brain fog of high levels I struggle to have the ability lower my levels and control my diet without a lot of support from family, friends and my metabolic team. The symptoms I have due to elevated blood levels have a detrimental affect on my quality of life asI feel unable to socialise with friends as I am too exhausted and I struggle to concentrate properly at work. There have been many times in the past that I have taken a weeks holiday from work so I am able to try and concentrate on getting my levels back down to a safer range.

Q6. I disagree with this as it has been proven that even with patients with treated PKU there is evidence of white matter changes on the brain. Personally as someone with classical PKU I know that my levels don't need to go much out of range to feel irritable, tired and easily confused. I do feel that having high phe levels in the past has had an effect on my life now as I feel that with a better and more reliable treatment I wouldn't have struggled so much in education or when I joined the workplace. I feel like these negative effects are holding me back from what I could have potentially achieved. I do feel this will continue to effect my future experiences as it takes me longer than the average person to learn things as I still feel the effects of brain fog frequently and my anxiety is very heightened due to following such a strict and restrictive treatment plan.

Q7. I believe there are many additional healthcare costs associated with health problems due to PKU. Personally as an adult I have received counselling for depression and anxiety, I have had appointments with a clinical psychologist and have been under the local eating disorder service twice. I am currently under their care and I feel that PKU has strongly impacted my diagnosis as I have huge anxiety when it comes to food due to having such a restricted diet. This has also meant that I have needed much more up port from my metabolic team, this has all been at the cost of the NHS. I feel it is very important to also take the extra healthcare costs into account when looking at the cost effectiveness of treating adults with PKU.

Q8. I think that NICE were wrong to not take into account the impact on other family members. Even as an adult family and friends support is vital, having the support of family is extremely important especially when the person with PKU is having symptoms which mean they are unable to stick to the treatment well. As a full time working adult with negative physical symptoms of PKU I have relied on family members to prepare meals for me and take the responsibility of ordering products to follow the required treatment. When I have blood phe levels that are too high I struggle to follow such a strict and restrictive treatment without the support of my family. My friends have to check that anywhere they are planning on taking us would either cater for our needs or allow us to take or own food so I am able to stick to the restricted diet. I rely on my mum heavily to prepare foods and meals when I have been working all day as I quite often feel too exhausted to prepare a low protein meal. I rely heavily on my partner's support to follow such a difficult treatment.

Q9. I feel that NICE's proposal is not treating people fairly, if what they have proposed was to be the final outcome it would be extremely discriminatory against adults with PKU. I feel that it is extremely unfair to recommend taking an effective treatment off patients when they reach adulthood. I do feel that if the cost of possible additional healthcare needs due to the restrictive diet and any problems relating to higher phe level had been taken into consideration in this proposal there would have been a different outcome. I think it is wrong to split adults with PKU into sub-groups, everybody with PKU deserves the chance to be tested to see if they would respond to Kuvan and then be able to have the best treatment available to them. I feel that to exclude certain groups of people would not only be discriminatory but also a failure of NICE and their decision makers.

Q10. I have been worried sincel was 14 about the risks that come with being a PKU woman and having a child. I feel that there is plenty of evidence supporting the negative outcomes of high phe levels to an unborn child and there is also evidence of Kuvan lowering phe levels of responders to a much safer range. The only treatment option we have in the UK makes planning for a pregnancy and being pregnant extremely stressful for women with PKU and their families, it is also a very difficult and even more restrictive diet before conception and during pregnancy. I feel that having an even more restrictive treatment than it already is would have an extremely negative affect on both the woman with PKU and her partners mental health and relationship. I also think that NICE have contradicted themselves with this statement as they have also said that high phe levels during pregnancy can lead to intellectual disabilities and birth defects.

Q11. I feel that the use of Kuvan would be a huge benefit to women of childbearing age as this would massively reduce the extra stress that comes with planning a pregnancy with PKU. Over the years I have been terrified of an unplanned pregnancy due to contraception failing and what

harm I could unintentionally cause an unborn chid. This has caused me to avoid relationships in the past due to the severe anxiety I have around this. I am unsure how I would cope with an even more restrictive diet than I have now which makes the thought of even planning a pregnancy in the future very anxiety inducing.

Q12. I feel that NICE should have included the cost of any child born to a woman with uncontrolled PKU as a child with maternal PKU syndrome would bring a lot of excess cost to the NHS. I feel if this was taken into account it would be clear that treating patients with Kuvan would be cost effective in the long term.

Q13. I have found that as I have got older and gained more independence has made me more aware of struggling to join certain social situations involving food, this has made me feel very isolated at times and unable to join in. I feel if I was t have the option to try Kuvan and respond to it my quality of life would improve rapidly. I think my stress and anxiety levels would decrease massively and I wouldn't need as much support as I currently am receiving and needing. NICE have stated that most patients are unable to achieve or maintain good overall phe control through dietary control alone but their proposal is not taking this fact into account when looking at adult patients. NICE have also stated that adults with PKU have higher rates of osteoporosis, gall bladder disease and other conditions which have been attributed to high phe levels and the consequences of a phe restricted diet. As I have mentioned NICE have said that most patients are unable to maintain good overall phe control through dietary control alone which will mean that PKU adults would have an even more increased risk of these conditions. European PKU guidelines state that decreased verbal memory and social and emotional difficulties are observed in PKU adults even when treated early so this proves that PKU still has an effect on the brain when the PKU patient is over 18 years old so an effective treatment should not be stopped. I feel that overall this proposal is extremely discriminatory and does not take into account the effects that the restrictive treatment has on the PKU adults throughout their lifetime.

Respondent 89

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. This is a catastrophe in the making. Transition to adult treatment and support services is patchy at best across the UK, with a lack of any coherent over arching approach and many lost to treatment at this stage. To further compound this patchy provision by introducing - and then removing - access to Kuvan at a key point in neurological development - and further more at a key point in education - is at the very least irresponsible and I would argue, entirely unethical. The so-called rationale for this decision is incomprehensible and shows a total lack of understanding and knowledge of the impact of PKU on the lives of patients, and their families/friends. Across the UK, adults across the age range from teens to those in their 50s (and later) are already suffering the consequences of poor access to best practice in treatment, compounded by a lack of knowledge in community/primary healthcare, and even those who manage to control the condition to a degree struggle with the time and wider health implications of a rare condition which is not well understood.

My own experience is that my teens was the time when I found management of dietary treatment the most challenging. I was very fortunate to be attending a clinic with leaders of good practice in the field and this and the medical background in my family ultimately kept me at least partially adherent. This is nothing more than pure luck and it is appalling to think of the harm that will be caused (and it is a cast iron certainty) by withdrawing access to a treatment known to work at this crucial developmental milestone both in terms of neurological development and personal development.

Q3. NICE's statements are contradictory

Q4. As previously stated in response to Section 2, I was fortunate in that my parents' education and medical understanding supported me in being able to continue to adhere to the strict and difficult PKU diet. However, I am all too aware of the issues related to long term brain damage, both for myself and other patients. On a day to day basis, I worry about what the future might hold for me and my family as a result of my condition. I am fortunate to have the support around me to enable me to adhere to a ridiculously strict dietary regime, but have found at several points in my life that even with this support and my own best efforts, factors beyond our control can have deleterious effects on my phenylalanine levels. For example, I became ill with suspected Covid-19 last year, and as a result, lost my appetite for several weeks. My phenylalanine levels rose as a result and because of the nature of this condition, I did not have insight into this fact until it was already too late. This hindered my overall recovery significantly because of the more subtle ensuing side effects - tiredness, lack of energy, headaches, 'brain fog'. All of these are of course common sequelae of Covid, but it was clear to see that mine were more severe than those of my peers, and longer lasting. I must live now with the fear that factors outwith my ability to control could potentially cause insidious damage to my brain function and in so doing, affect both myself, and my husband and children. Furthermore, the immediate mental health effects (forgetfulness, confusion, irritability) affect my family life and relationships and my closest family members - my husband and children - have to live with and manage this in order to support me. There is no acknowledgement of this burden of care for patients and their families/friends and the consequent impact on their lives. My children are not registered as carers, my husband is not registered as a carer - and yet, they carry a much heavier load than their peers as a result of a medical condition that I inherited via a faulty gene. Unasked for, and unexpected and pretty much entirely unacknowledged by society in general, and frustratingly, frequently dismissed and played down by the medical professionals who treat us.

Q5. I absolutely recognise all of these side effects and find that there is a very clear correlation between my Phe levels and my ability to manage in day to day life. I tend to anxiety and overthinking at the best of times, and in my role as a secondary school teacher, this effectively cost me my classroom career. As a result of the challenges of managing the PKU diet through pregnancy and into the early post natal phase, I had to give up a job I loved and was very good at doing (my lessons went from being judged as Good/Outstanding in pre/early pregnancy) to Unsatisfactory). There was zero support for me (or my family) as a new parent - I went from 3 *[no response given to this question]* weekly contact with my clinic, to nothing at just the point I needed that support the most. I was looking after baby twins, trying to hold down my job and manage our family life/home and just could not do it all. I have no doubt whatsoever in my mind that had some kind of treatment and support been available to help with alleviating the effects of high Phe, I would still be the Outstanding Teacher I was.
More subtly, I find the effects of high Phe to have worrying effects on my quality of life even now day to day - it's much harder to concentrate and co-ordinate, so I avoid driving on long journeys. I choose to stay closer to home and miss out on opportunities further afield - which impacts on my children too.
Worryingly, once one is in a spiral of high Phe levels (and bear in mind that Phe levels can rise due to illness, loss of appetite, hormonal variations - factors we cannot control), it is extremely difficult to bring them back into line. Tiredness and brain fog means I find myself reaching for 'easier' food - for me and my family, bringing the possibility of future health effects on my children too.
There is no doubt in my mind whatsoever that having PKU and the consequent impact on my mental and physical health means that my family

and I suffer from a poorer quality of life.
It is established that families of those with disabilities of any kind face structural barriers of many kinds and a lack of access to potential treatments (and the resulting implications of the judgment that we as adults are 'not worth' the investment) mean that there is a total lack of equity of opportunity for those affected by PKU. Denying, or limiting access to medications which can help is ethically unexcusable.

Q6. As per my response in Section 2 (symptoms and quality of life), it is clear to me that the impacts on quality of life MUST be taken into account when calculating cost effectiveness of treatment for adults. If I had been able to continue in my career, I would still be working full time, and earning a great deal more than I do now. (approximately 4-5 times!) The increased revenue from my tax and NI payments seems not to have been considered, nor the cost of medications to treat the co-morbid conditions I suffer as a result of PKU are not considered either. Nor does it seem that the reduction in costs of Special Medical Foods and time/opportunity cost of the administration and issue of prescriptions and food and other products has been considered either. (NB NOT supplements)

Q7. It is entirely unclear whether costs surrounding Maternal PKU have been considered at all. Increased visits to GP, increased prescription requirements for Special Medical Foods and treatments for eg nausea, reflux, and calorie/nutritional support (and associated administration). There are also costs associated with more frequent Maternal/antenatal and PKU clinic visits/blood tests/assessments - and opportunity cost in terms of time lost to all of these requirements too.

Further, I suffer with eg acid reflux for which I have required medication and investigations over several years.
I have required more GP/nurse clinic visits over the years than most 'average' patients, both for physical and mental health reasons.

Q8. As previously stated, living with PKU has had huge effects on my life. I have had to walk away from a successful teaching career as a result of high Phe levels and continue to suffer limitations on my ability to work full time and manage my family. Further, my husband has made career choices which have been impacted by my needs - we have been unable to avail of wonderful opportunities to live and work abroad because of the complications of having PKU. My children are de facto (unacknowledged and unrecorded) carers because they have to manage living with me and my needs.
Furthermore, having PKU has had immense effects on my parents - my mother was forced to stop working altogether in order to manage my condition. This has impacted on our relationship as well, due to the (totally justified) resentment and frustration this caused.

Q9. It is abundantly clear that NICE has taken absolutely no account of equitable treatment for different groups of people who may have difficulty managing - or even accessing dietary treatment.
The high incidence of PKU within eg communities with Irish/Scottish ancestry, Roma/Traveller backgrounds has not been acknowledged at all.

And for women with PKU there has been zero recognition of our needs as a group and we are disadvantaged at every turn. My entire adult life has been dominated by an absolute terror of an unplanned pregnancy - and even when I was fortunate enough to have a planned pregnancy, this was haunted by the fears of the potential consequences of MY PKU on my children. Due to the appalling mess of adult transition and lack of coherent support for adults across the UK, there are many women in an unrecognised position of managing the effects of Maternal PKU on their children. Even in my own (planned and successful) pregnancy, the separation of ante natal treatment locally from my PKU clinic was frightening. It wasn't until 16 weeks into my pregnancy that my local ante natal services realised I even HAD PKU or took any action to ascertain that my PKU was treated/controlled. This is TERRIFYING and an utter disgrace.

Once again, it is abundantly clear that no account whatsoever has been taken of equity of access to treatment for those disadvantaged whether by gender, race, or ethnic group.

Q10. I wonder where the committee actually looked for evidence? Or did they even seek any?!

The fact that Kuvan is prescribed in some circumstances for women when the risks of Maternal PKU require it means that such evidence exists. And if it's not easy to find, why not launch a trial or study to establish some evidence?!

Q11. From my own experience - one successful, planned, twin pregnancy, and one unplanned and failed pregnancy which ended in a miscarriage at c.6 weeks - the idea that Kuvan could potentially have prevented harm to my children is unbearable. My twins are now at secondary school, and so far are following mostly normal neurological development pathways, although my son does have some auditory processing issues. His teachers have been able to manage this - but this means extra work and allowances (and consequent costs) within the system. My successful twin pregnancy would have benefited greatly from access to Kuvan. I suffered severe morning sickness for 16 or so weeks, and lost a good deal of weight (to the point that I weighed less at the end of the pregnancy than I did before). By a supreme effort and huge amounts of support from my husband and family - and finishing work early at 28 weeks - we were able to control the Phe levels but the stress and trauma of the pregnancy remains to this day.
The miscarriage I suffered at 6 weeks will haunt me for the rest of my days - was I responsible because my levels weren't low enough? Again, I suffered extreme nausea right from the moment of conception pretty much and as the pregnancy was unplanned we weren't immediately aware of the cause and the need to reduce my Phe levels. Access to Kuvan throughout my life could have saved a great deal of heartache for me and my family.

It is difficult too to quantify the effects on my relationship of living in permanent fear of an unplanned pregnancy.
I have also spoken above of the impact of high Phe levels postnatally. Again this was due to factors outside my control. A diffcult and traumatic delivery involving a huge haemorrhage left me in need of HDU care for several days after and in hospital for 12 days post delivery. In addition to this, the food provided by the hospital was so unsuitable for my needs - no account was taken of my low protein diet whatsoever - that my family were reduced to bringing my meals to me. This undoubtedly added to the length of the stay I required (again financial implications too!) and impeded my recovery significantly. This continued to impact my ability to care for my children throughout their first year of life and ultimately impacted my ability to work full time in my previous role. This has never been acknowledged and it is clear that access to a treatment such as Kuvan could have prevented at least some of this trauma is very clear to me.

Q12. This fact makes it very clear indeed how little NICE, and all involved in this process understand about PKU as a condition. It compounds the day to day difficulties of living with this type of invisible disability and is very difficult not to take personally as a judgment on our value as human beings.

Q13. The draft recommendations are riddled with inconsistencies and inaccuracies and it is very dispiriting indeed that after 13 years in which Kuvan has been used in countries across the world to read that there is 'no evidence' of its benefits - something which is easily disproved by even a brief discussion with actual patients suffering with PKU and the effects on their lives. Patient voice is crucial and must be listened to.

Respondent 90

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I feel that this proposal seems to be decades out of date, and seems to go back to when I was growing up becoming an Adult with PKU when I was advised by my Doctors that I could come off diet because my brain would stop developing by the age of 12 and therefore there is no damage which can be done after this time. Firstly this was an upsetting promise to be giving a young child, that when they became of a certain age any deleterious effects would somehow suddenly stop. Thankfully this train of though was updated during the 1990's to understanding that this is a condition for life, and not something which is only a childhood condition. Diet for Life became the leading advice from the medical profession for a reason. This is why I find it incomprehensible that NICE has made this proposal, as it seems to take us back to when I was a teenager in the 1980's. At the age of 18 I was starting University, something that was only possible because I didn't follow the advice in the 80's that PKU was merely a pediatric condition, but required dietary management all my life. I know how tough it was then to be able to manage my diet and ensure I studied for my degree, and being on Kuvan now I know how much of a difference this would have made to my quality of life during this time - as it surely will do to countless PKUs of this age now and in the future. This is before I even mention Maternal PKU, which I'm sure others will mention but just puts this into even more perspective as to what a dangerous proposal this is, never mind one that will almost make the quality of life even worse for those individuals who are on Kuvan until the age of 18, and then suddenly have to adjust to life without it. It just doesn't make sense. Even the argument of the dosage being based on weight, and therefore the whole treatment becomes less cost effective is weak, as it is based on 40 year old rhetoric of how the condition of Phenylketonuria effects individuals which is just simply wrong but also there is countless medication which is similarly administered, so I am sure NICE have come across this before when deciding on providing treatment beyond the age of 18. I have first hand experience of performing poorly in my career at times of poor dietary management, and it is of no coincidence that the most successful parts of my career coincide with when I have been on Kuvan to help my dietary management - firstly during the trial in the mid-2000's and right now after Biomarin have agreed to provide it since October 2020. I am 48 years old and have had to keep to a restricted diet through most of this time (other than when I was on Kuvan), and I have also had the opportunity to see the positive effects of Kuvan on my quality of life so I know what a difference this will make not just to children but also to adults.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. Absolutely. Whilst I was working working for a pharmaceutical company in the 1990's as part of my degree I was working on a helpdesk for PKUs and had a call from a distressed mother from the US who said that her son had, as had been the advice in the 1980's , come off diet and had been off diet for 12 years - he was in his mid 20's. He had suddenly become paralysed on his left side, and the demyelination had reached a critical point. This was attributed to high Phenylalanine levels. This is one of the aspects of brain damage which occurs in adults, damage to the central nervous system (CNS). I have also have a brain scan and even with dieatary management (which was not a good as if I had been given Kuvan during my young adulthood) my brain had elements of damage to it. This again is something which is widely accepted in the PKU commuity, medical and family based so again it really does surprise my that NICE have referenced what seems to be the still outdated references in medical school lectures that PKU is a Pediatric condition and all patients have already had brain damage by the time they are young adults and there is no treatment for it.

Q5. I can absolutely relate to this, and this brain fog and inability to concentrate is the reason for the poor performance at work over the years when I was still trying to maintain my diet and not being on Kuvan. My tiredness had also been an issue before and the quality of life measurably increased when I was on the trial for Kuvan, as these symptoms almost disappeared.

Q6. I really don't understand why it would not be relevant - it is absolutely relevant for the reasons I have already noted. To simply disregard the evidence that PKU keeps on effecting people beyond the age of 18 is outrageous. What suddenly happens to the body that it can cope with high levels of Phenylalanine and there are no toxic effects which effect the quality of life. There are countless ones, the most stark being job performance, mood swings, ability to entertain friends more easily, ability to eat out, ability to go on holiday - all these would be difficult for an Adult maintaining the diet without Kuvan. I know because I have experienced it for the last 48 years! I am lucky enough for this not to have affected my mental health but I know of many individuals where it has, and this has to be a consideration for NICE.

Q7. Absolutely this should be a key consideration for NICE when looking into the overall recommendation and shouldn't be ignored. A lot of side health issues stem for poor dietary control not to mention the psychological effects we have already noted, something which is costly to the NHS and to society.

Q8. Yes definitely and I know my wife would concur, especially with respect to my mood swings when I was taken off Kuvan after the trial. We were recently married, and she hadn't know me as a PKU on diet with irritability, tiredness,, inability to concentrate not to mention the difficulty we had in the dietary aspects which she had to suddenly get used to.

Q9. How can NICE suddenly disregard the unequivocal acceptance that the unborn child is damaged by poor dietary control and in one part acknowledge this and in another say that the cost is too high to warrant the recommendation. Think of the cost of a mentally retarded baby to the NHS, let alone the moral obligations. This is simply unbelievable.

Q10. This is again going back to the 1980's - there is a lot of evidence to show that low phe levels reduce elements such as microcephaly which has been common as well as severe development challenges. NICE should further review this and ensure that over 18's can benefit from Kuvan and especially mothers requiring to go back on diet and maintain very low hard to manage levels.

Q11. I am obviously not someone who is affected by this directly, but I have kept up to date with currently medical research on PKU since the 1980's and know that this is a very real issue medically before we even go into the psychological aspects that I know some people have and continue to have in the PKU community. This is a very real issue which NICE is just sweeping aside as non-important - how do you expect these women to feel?

Q12. This is something which absolutely needs to be included for any accurate cost benefit analysis to be achieved.

Q13. I am more than happy to discuss my experience further, and the fact that I am an older PKU which has had the experience of maintaining dietary control all my life, whilst also being on Kuvan for 5 years and then another 6 months now I feel I am very qualified to speak for many others with PKU. I am very disappointed with the recommendation currently given and I hope that this will be over turned so that all adults will be able to benefit as I have, and at least that expectant mothers will be able to at the very least. You need to do a more thorough cost benefit analysis based on up to date knowledge, not old out of date rhetoric from the 1980's where I feel we have now gone back to with your current recommendations.

Respondent 91

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Nightmare for one day after aged 18 why would thou impose such pain and lethargy and completely restrict food intake why?

Q3. I do not agree with NICE's view;40 year old has to maintain diet, or just can't function

Q4. Friend was so ill, affecting memory and general day to day abilities
Was working full time but had to resign

Q5. I'd repeat all those comments- try holding down a job or parenting with those feelings

Q6. Quality of life is affected in all aspects

Q7. A person had to be educated in Wales because they were expected to fund £80 prescription foods with no income If educated in Britain.

Q8. No. It's a nightmare feeding and satisfying hunger

Q9. You can't not let up from managing phenylalanine levels. One days lapse leaves a brain fog

Q10. Prescribe kuvan

Q11. Managing your own day to day unsupported by kuvan, why would you happily get pregnant knowing you are going to feel ill all the time? Or hungry all the time

Q12. Costly in the longer term

Q13. *[no response given to this question]*

Respondent 92

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Personally I found the diet hardest around the age of 18 due to changes in my personal life that also many other young people experience, such as moving out, usually with housemates and peer pressure, lack of access to the right equipment and money as well as starting education and being independent / working for the first time. This is already a difficult stage and was impossible for myself to carry on the diet at that age. This is without the addition of being told to follow a diet unknown to them for the first time in years, as far as some will ever remember they will have been taking Kuvan. This will surely lead to poor education and work attainment in a world where it is already more difficult for those with PKU, myself including, to adapt to a independent lifestyle where every day is a battle to manage a combination of societal expectations that don't fit in with the life of someone with PKU.

Q3. I do not agree with NICE's view;NICE's statements are contradictory;The brain never stops developing.

Q4. In my experience brain damage does not stop at any age. My memory, cognition and thinking patterns have deteriorated throughout my life. My focus and attention span is the worst it has ever been at the age of 28. As a child I loved reading and read all the time, now the words don't go in and I find myself reading re-reading the same page over 10 times before giving up as my brain cannot process the information. I re-watch TV to understand simple parts of the show and I cannot retain information I have just tried to process. My mind jumps from one topic to another and I cannot finish tasks. My mental health has deteriorated throughout my life, with severe anxiety, agoraphobia and panic attacks all associated with PKU.

Q5. High phe levels are all encompassing and hinder everything in your life. Brain fog and lack of attention affects employment and education. Confusion and memory problems also impact day to day life where simple tasks become impossible. Mental health problems such as anxiety, phobias, panic attacks and depression all worsen these effects along with lethargy. I also suffer with severe gastrointestinal symptoms attributed to the PKU supplements, so much so that I have been advised to stay off the diet by my consultant and dietician as there is no way I can do the diet safely. Gastrointestinal symptoms such as vomiting, diarrhoea, indigestion/heartburn and abdominal pain is chronic and severe, to the point where this alone makes it impossible to function normally in society. I have peripheral neuropathy caused by high phenylalanine levels and when my levels are really high, I can tell because my mobility becomes affected, specifically in my leg due to pain, numbness and instability. I also suffer from frequent migraines directly related to high phe levels and can be a daily occurrence. Due to the fact I am not advised to be on diet under current NHS guidelines, I starve myself if necessary food groups to enable myself to function at a basic level, however this is simply existing difficultly.

Q6. Having high phe levels definitely impacts of future health and life experiences, shown by my worsening mental health, disordered eating, thinking patterns and my lack of achievement in life such as poor education attainment and difficulty staying in a job.

Q7. I believe substantial costs come from treating illnesses that are due to having high phenylalanine levels. I personally have seen neurologists, gastrointestinal team, psychiatrists, psychologists, counsellors, support workers, increased GP visits and prescriptions for migraine, general pain and tiredness, increased blood tests and *[NO RESPONSE GIVEN TO THIS QUESTION]*-rays due to pain in body. All additional costs to the NHS that are attributed to high phe levels.

Q8. *[no response given to this question]*

Q9. NICE has not treated people fairly. In my experience with ‘gut’ problems attributed to PKU, I am unable to take GMP based formula due to a dairy allergy. Amino acid based formulas are the only other option and are incredibly difficult to digest. To take amino acid formula I have to take a combination of other medications to stop vomiting however these medications do not stop other symptoms such as diarrhoea, indigestion, abdominal pain and extreme stomach gurgling. It is not possible to function day to day and leave the house with these symptoms that are equivalent to having norovirus every day of your life. Therefore I have been told I should not follow the diet, meaning the NHS does not offer me any treatment for my PKU as the limited choice it does offer discriminates unfairly based on my health.

Q10. NICE should offer Kuvan to women of childbearing age due to fear of becoming pregnant and potentially damaging to health of their future baby.

Q11. I have no children due to the fact I am unable to have low phenylalanine levels due to my inability to follow the diet. The potential failure of contraception is something I worry about frequently as I would never like to be in a situation where I have to think of my future child’s life with multiple health problems when this is completely preventable using Kuvan.

Q12. Maternal PKU syndrome can come with high costs due to the possible health problems, defects and disabilities that they will potentially suffer with throughout their life. This would be very costly and should be taken into consideration.

Q13. PKU adults struggles to adhere to PKU low protein diet due to various factors should not be invalidated. The PKU diet is not a diet, it is a change of life that is not compatible with modern society and daily functional living.

Respondent 93

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Being a teenager with pku is very daunting. When you start to get independence and go out with your friends, go to college or move to university, you have to take on a huge amount of responsibility with managing your diet. From my own personal experience, after living at home until 18, my mum was there to help and guide me with my diet and I had everything available to me. It’s not until you start to become independent you realise how difficult it is to manage and how hard it is to eat out, how difficult it is when doing a food shop and having to check the back of literally everything you are buying. Cooking becomes daunting and it’s so much pressure as you always have your health at the back of your mind. When I moved to university it became so much harder to control. Your routine gets thrown out of the window, you are becoming an adult and making decisions for yourself. Having pku can quite often be a burden and you feel left out of so many social aspects because you can’t eat certain things and always feel guilty or like you’re being difficult and it can really get you down. Alongside with having high levels that can heighten anxiety. I know being a teenager, a young adult is hard in itself, you are under a lot of pressure and go through massive life changes and milestones, dealing with the effects of high phe levels like brain fog, anxiety, tiredness etc is really hard. All of this whilst trying to fit in somewhere completely new and also make sure you are studying to the best of your ability. A lot of college/university/job and working environments are centred around the social aspects of it, often surrounding food, and having pku and trying to maintain your diet can often be a hindrance. I know that sometimes you feel really isolated and like nobody else understands how you feel. If KUVAN was given to those over 18 I know personally the pressures of trying to control your diet, whilst also trying to find your way in the world and become an adult would massively help. It would give adults so much more flexibility, as when I was a child, as naive as it sounds, I didn’t have to worry about my pku as my parents did it all for me. I am so grateful for that now as it’s so hard to navigate. Eating out, cooking, doing a food shop, paying for prescriptions, organising your supplements, affording low protein foods, planning pregnancies etc, it’s a lot for someone to deal with. If there was a way that pku could be easier to manage, it is so important that it is considered. When I was 18, 10 years ago, if there was an option of KUVAN available, obviously it would have made my childhood easier, but as an adult and making all of these decisions for yourself, it would literally be life changing.

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. *[no response given to this question]*

Q6. *[no response given to this question]*

Q7. *[no response given to this question]*

Q8. Pku has a huge impact on other family members and those around you. It dictates so much, places you can/can’t go, family life at home e.g cooking separate meals, food shopping being such a daunting stressful and expensive task, mood swings/anxiety/physical health due to high levels affecting other people, dictating travel and holiday options, women with partners having to deal with the pressures of pku and pregnancy. Pku doesn’t just affect the person who has it, the whole family is impacted and has to adapt to it without any say or anything they can do. It just has to be dealt with. If kuvan was available the pressures it would take off families would be huge!

Q9. *[no response given to this question]*

Q10. There needs to be more research done by themselves to look at the risks that managing maternal PKU can have on an unborn baby. There is so much that girls with pku have to consider with pregnancy, and if there is a way to prevent or help that, then they will be helping so many women and babies have healthy pregnancies. Stress, anxiety, pressure and worry are all things which a pregnant woman shouldn’t have to deal with, but then having pku and adding all the risks with pregnancy and diet, is so much for one person to handle. If this can be helped then I do not see why it shouldn’t. KUVAN for over 18s, in this case for women, would be life changing.

Q11. From a young age I have had it drilled into my head of all the risks that high phe levels could have on any baby that I may carry in the future, and that I need to be extra cautious in every aspect. E.g being extra careful with contraception, being extra careful with diet, what I would do if an accident happened, how I would get my levels down if it did happen, all the extra care I would need to take if I were to carry a baby. All of this, alongside the usual anxiety that comes along with a normal pregnancy is a lot for women with pku to handle. The fact that we are advised to plan our babies so they could have the best possible outcome, to change our diet and then worry about every single thing we are eating, to

try and control getting enough calories in, worrying if baby is healthy, and if they aren't healthy is it something that you could have prevented, is it your fault because of what you ate? All of this is so much, and the stress/worrying isn't good for any woman carrying a baby. If women with pku carrying a baby had access to KUVAN and could relax their diet even slightly, they would have so much more flexibility and wouldn't have to panic as much about everything they are eating, about the pre conception diet, and it wouldn't be such a daunting and frightening experience. I know from my personal anxiety surrounding it and having pku myself and being in my late 20s, I have so much built up worry hoping everything will be okay if I am ever lucky enough to carry a child. The people at my own clinic and dietitian's have been nothing but kind and helpful, but there definitely needs to be more support to try and make this an easier and less scary experience for girls with pku. My older brother also has pku and from being very young the clinics would always focus on making sure that I was aware of everything to expect when I was older and the things I would face having a baby. His experience was totally different as he didn't have the fear about what could happen. If KUVAN isn't an option for those over 18, I know there will be so many young girls like me who have this huge amount of pressure on their shoulders surrounding pregnancy, if KUVAN was available it would be a massive relief for women with pku including myself. I dread to think of all those young female babies and children with pku now, who will grow up with the same thoughts that I do surrounding the topic. Knowing that there is something out there that can help, but it isn't available to them is soul destroying. Pregnancy and the health of your baby is such an important thing and should not be overlooked, the risks that having pku could have on your babies health should be something that is considered as vital when deciding on whether KUVAN should be available for those over 18. Obviously I am aware happy and healthy babies are born to girls with pku, but the whole daunting experience and pressure should not be unnecessarily inflicted if there is a way to prevent it and help all girls that go through this.

Q12. Why wouldn't they include the neurological damage to the children with women with pku? Why would this not be a factor! That is SO important!

Q13. Having pku as an adult 100% affects life experiences. It is always something that needs to be considered e.g is there something for you to eat if you aren't at home, eating out, where you work, transporting supplements, travelling. Going on holiday can be one of the most daunting and stressful tasks. You have to worry about foods/supplements, airports and providing letters and evidence. Can you go travelling or somewhere for a long trip and will you have access to your supplements? Will there be food you can eat without feeling poorly? If I run out of supplements will I feel poorly? Will I be able to eat my foods at work?
It can stop you wanting to go somewhere because of the issues you will face. If this can be relaxed and helped by kuvan for adults then it would massively help adults in every way. The mental and physical affects that having high levels can have on a person can dictate that persons whole life.

Respondent 94

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I feel it is cruel and discriminative to expect a child that reaches adulthood , to brain damage themselves by continuing to eat a diet they have been accustomed to as a child, because of a genetic disease they were born with.

Q3. NICE's statements are contradictory

Q4. Listening to the PKU community, lots of adults who came off diet are now dealing with awful neurological consequences.

Q5. My son suffers with anxiety during times of high levels.

Q6. Yes I agree.

Q7. My child has severe gut issues and is under a gastroenterologist. He takes medications due to acid reflux. I feel this is connected to his supplements.

Q8. *[no response given to this question]*

Q9. I dread to think what it would be like to have to force a child/person with sensory problems, to eat a food or necessary supplements that distresses them.

Q10. To give all PKU patients a trial of KUVAN. With responders to stay on this for life.

Q11. *[no response given to this question]*

Q12. If we could prevent this, why wouldn't we ?

Q13. As a parent, my worst nightmare is my child coming off diet at any age. The future is uncertain for our children and adults. Many are suffering and it is in humane to ask a child to go back to a very restrictive diet and supplements at a certain age.

Respondent 95

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Bad idea. As a child I was always monitored closely by my parents. After the age of 18, I was experiencing different foods even when I knew I shouldn't whist out with friends just to look normal.

Q3. I do not agree with NICE's view

Q4. I can get brain fog. I'm not really a quick thinker which knocks my confidence for things like job interviews, confrontations etc

Q5. I do get brain fog sometimes and everyday tasks can be overwhelming ie having a conversation. I can get headaches and upset bowels. It can be hard just to digest these questions to answer them.

Q6. No Information for this but it's definitely something I worry about in day to day life.

Q7. I suffer with IBS through me being pku.

Q8. I definitely think the should have. Of course it effects other family members. It limits you in everyday life.

Q9. Not at all. They act like there’s millions of us! Pku is a rare condition.

Q10. N/a

Q11. N/a

Q12. N/a

Q13. We are already already deprived...

Respondent 96

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. i find this recommendation absolutely stupid why give it to children under the age of 18 and not adults it doesn't make sense and what your saying is a child can have kuvan up until the age of 18 then stop kuvan on their 18th birthday they are going to be used to having the right to have a normalised diet then on their 18th birthday told they have to return to strict pku diet and having to take horrid supplements and again struggle with birthday parties, socialising and meals out me as a pku sufferer would love the opportunity of taking kuvan it would change my life completely i work in the nhs and i find this is a act of age discrimination and i may be returning to my face - face role soon where my supplements are a constant battle having to mix supplements and drink them and having the time to take them where taking kuvan would be easier and less time consuming

Q3. I do not agree with NICE's view

Q4. i would just like to add some one over the age of 18 is just as likely to suffer brain damage than someone under 18

Q5. when my phe levels are high i experience really bad headaches that sometimes last for 4-5 days tiredness and my hands sometimes shaky headaches that dont go with pain relief i am on gabapentin 600mg gabapentin 100mg nefopam 90mg daily and ibuprofen paracetamol for problems with my back and hips which again is associated with pku and again doesnt control the headaches so im asking you to reconsider your recommendations for kuvan in adults over the age of 18 years

Q6. i think regardless of cost every pku sufferer should have the right to take kuvan

Q7. acid reflux is a big problem

Q8. when i was a child my mom used to weigh my pku exchanges out in resturants cafes etc my dad walked out this is because my dad does not understand pku as much as my mom which made me sad upset but also its time consuming to make meals up mix the supplement and being questioned about my food etc at work and i still feel embarrassed

Q9. no i do not but ive heard kuvan isnt safe for pregnancy i have heard of people taking kuvan whilst pregnant but surely there is a way forward for making kuvan safe for this category

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 97

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I speak as a mother of a girl with Clasical PKU now aged 27. The hardest time to manage the diet was when she turned 18. Moved from child NHS services to adult services with a huge drop in clinical support. As a parent I spent my life encouraging independence in managing the diet. The transition from school to work left her exhausted and unable to manage the diet. She had a breakdown in mental health. 18 is a very vulnerable age and to withdraw diet at that time will have devastating affects on mental health.

Q3. I do not agree with NICE's view;Poor dietary complience has caused further brain damage since aged 18 brain damage in

Q4. My daughter continues to struggle with dietary compliance has poor concentration.gets over emotional and work spirals out of control.

Q5. I see that in my daughter. She wants to work. Has an entry level admin job but has no energy left for anything else. Home life poor. House a mess. Cooking erratic. Minimal social life. Constantly tired and irritated.

Q6. Not taking into account long term effects of high phe levels is to consign her life to the dustbin

Q7. Long term mental health issues and inability to contribute effectively to society. Daughter receives personal independence payments and is reliant on benefits system.

Q8. I had to continue as carer after pku daughter was 18.

Q9. I was caring for pku person as a single mother because father could not cope with child with pku. Low income. Daughter now married. Wants to start a family. Cant cope with going on the level of diet needed to prevent damage to unborn child. Constantly worried she might get pregnant by mistake. Destroying her marriage.

Q10. Should definitely recommend as part of preconception diet. Pku daughter is unlikely to have a live born child due to struggle to comply with diet. Cant cope with going on the level of diet needed to prevent damage to unborn child. Constantly worried she might get pregnant by mistake. Destroying her marriage.

Q11. Cant cope with going on the level of diet needed to prevent damage to unborn child. Constantly worried she might get pregnant by mistake. Destroying her marriage.

Q12. Cant cope with going on the level of diet needed to prevent damage to unborn child. Constantly worried she might get pregnant by mistake. Destroying her marriage.

Q13. Nice have totally underestimated the effects of dietary control on lifestyle of over 18s particularly girls who want a family.

Respondent 98

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I think by stopping treatment at 18 you will have a whole generation of teens who have ko idea how to manage a very restricted pku diet. You already feel different as a teenager without having to deal with a whole new diet too

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. My husband has pku and he was born in 1969 when all of this was very new. He did not have consistency of treatment and this has left him with permanent damage and some learning difficulties.

Q5. High phe levels not only impact the sufferer but everyone around them, it causes uneven mood swings, anxiety, aggression and lack of sleep and inability to function properly. It impacts their job and their family life

Q6. *[no response given to this question]*

Q7. My husband requires b12 injections every 3 months. There are costs for supplements and prescription foods and as they age there are other health related costs surely the costs of supplements, the constant hospital appointments, consultant and hospital costs and blood analysis every month, food and vitamin deficiencies could be offset against the nice costs

Q8. Yes. I manage my husbands diet almost completely, I order all his low protein foods and supplements, I shop for his regular food which is not a easy task with label reading and weighing. I do all of our family cooking so I have to cook two separate meals each evening along with weighing everything and working out all protein contents. My children missed out on some time with their dad when they were small as he is sometimes too tired and not physically able to take part in all things with them

Q9. The only way to treat people fairly is to allow all people the same access to this drug.

Q10. Surely maternal pku is when you most need management to prevent harm to the unborn child!

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. Please give us the chance to have a more normal life, I want us to be able to eat together as a family without considering where we can eat to accommodate the diet. I want to be able to go on holiday without having to take a suitcase just for prescription foods and being questioned by the authorities about what you are carrying. As we have all learnt through covid it is the small things that really matter

Respondent 99

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I myself do not have PKU, however, my very close friend of 12 years does. I have seen her struggles both as a 15 year old and now as a 27 year old. Children under the age of 18 tend to have more guidance with their diet, needs and have help readily available; a fact supported by the recommendation for treating people with PKU under the age of 18 with Kuvan. I feel it has not been accounted that the years after 18 are some of the hardest in your life, and even harder to navigate when you have a lifelong condition such as PKU with currently has no cure. To add to the mix, the brain damage caused by exposure to protein has lasting effects and can also inhibit some people with PKU from fulfilling their full potential; due to tiredness, concentration, bad memory…the list goes on. After the age of 18 is when people gain more freedom, and with being on a restricted diet for all of their lives, people with PKU (in my experience) tend to want to experiment, yet there is always a restriction. This restriction is not only purely dietary, but also limiting socially and mentally exhausting. Remembering to take your drinks or tablets at regular intervals is hard, but remembering to take them when you have PKU is even harder. I believe after the age of 18 is when it is more crucial to be given the tools to fulfil your full potential, start a career, have a family (another mentally and physically draining scenario that happens for women with PKU), and I believe that Kuvan would help people with PKU fulfil this, or at least aid them. I do not think that having a lifelong illness such as PKU should be debilitating and yet it is in so many ways. I have seen my best friend's weight fluctuate from coming on and off diet, the stress of her dietician's pressuring her to do better but with very limited help and guidance, the low quality of food available for her "special" diet, and the draining effect of having to constantly measure food, measure protein and points and make sure she has her drinks/tablets at regular intervals, as well as the social aspect; her PKU sometimes made her outcasted at school, and she has had comments in the workplace before. She has missed out on doing so much throughout her life, due to inadequate support from professionals, and the lack of medical medication and research. Fortunately, she does have very supportive parents, but imagine if a young adult/adult did not grow up with the same support and structure. And if somebody like my best friend struggles on a daily basis to live her life, to deal with the tiredness, the brain fog, remembering to note her diet and points, then how would this effect an adult who has not had the same support when younger, and

does not have access to a potentially life changing drug such as Kuvan.

The pressure that somebody who has been on Kuvan all their life would feel to know that the moment after their 18th birthday their medication is going to be stopped would be terrifying. What would it result in? I understand the importance for the medication in children up to 18, but I also stress the importance that the medication is needed for adults. It is not an illness that will just go away. If not properly monitored, as you know, it can result in serious consequences.

Q3. I do not agree with NICE's view

Q4. After my friends birth it took her 17 days to be diagnosed with PKU. This resulted in her having mild brain damage due to her being breastfed. This has had an effect on her, especially at school. I truly believe she would have been able to achieve much better grades had more research and better medication been readily available. She was given regular breaks, extra time in exams, a laptop to help her complete her work due to her poor handwriting and was regularly observed. Whilst she was given support throughout school and college, since completing her studies, her support has diminished. Being an adult leaves you on your own; independent and vulnerable, with little to no guidance. The limited or in some cases unknown understanding of those who do not have PKU is shocking, due to it being such a rare condition. My friend has dealt with mental health issues and learning difficulties, some that we truly believe and have been shown to have been caused by her brain damage. The services available to adults with these difficulties is little to none. The brain is still developing until the age of 25 – a time that my friend struggled to stick to her diet, really struggled with her mental health and getting into a regular routine, having had her once stable world taken away from her at the age of 18. NICE states there is no risk of long-term brain damage in people with PKU over 18 but I just cannot agree, and to add to the mix what about adults who have brain damage as a result of late diagnosis, and already feel the effects of brain damage. I feel they are being left open, vulnerable and exposed with no help – help the Kuvan drug would really provide. The NHS states there is “not yet any evidence that high phenylalanine levels caused any brain damage” the key words being “not yet”. The focus of adults not being at risk to further brain damage, I feel, is being used as a scapegoat to avoid looking at the real issues of living with PKU such as dietary restrictions, serious effects if coming off diet, brain damage, behavioural and mental health difficulties, tremors, epilepsy to name a few. The increase to quality of life that could be given by children and adults taking and being access to Kuvan would be life changing.

Q5. As my friend is classed as Classical PKU, she has a very low tolerance to phe. This has meant that she has to follow a very strict diet, stricter than most. This has had a profound on her mental health, especially around the ages of 16-26. At the age of 27, she has now only just started to find her feet in terms of maintain diet and having lower blood levels, however, her blood levels are very inconsistent. With blood levels needing to be below 600, but regularly above it has had a huge effect on her everyday life. The tiredness and brain fog can sometimes lead her to feeling lethargic and unable to motivate herself to cook, and think clearly. This then leads her to become more irritable, upset and for her mental health to decline. I have witness this cycle happen on a weekly if not nearly daily basis. It seems no matter how hard she tries there is always a roadblock such as brain fog or short term memory to tiredness, that she has to overcome. These effects of PKU seem to be even harder for adults. Running a household, holding a job, remembering basic errands and appointments to remembering birthdays and special dates, as well as remembering drinks, tablets, diets, point taking is exhausting, and something that will be with her for life. The constant fog, irritability and pure frustration she feels is draining. I feel these effects really are debilitating and we often wonder what “could have been’ had a drug such as Kuvan was made available not only for children, but for adults.

Q6. I think it is unjust, immoral and dangerous not to take into account the long term effects of high or low phe levels in adults, especially if the people discussing this do not have PKU themselves. PKU is a lifelong illness without a cure. It is immoral to expect people to live their lives through a fog, never reaching their full potential, especially when a drug such as Kuvan is readily available if it wasn’t for the cost. PKU should be treated as seriously as any other lifelong illness, and yet is not. The lack of support available, especially for adults is so limited. Now take into account the fact somebody has PKU. The long term effects DO effect the quality of life in adults, and it is unjust and appalling not to take them into account. my friend has had the following when high levels of phe: brain fog; leading to limited function during the day, short-term and long-term memory loss, making mistakes at work, not being promoted at work due to these effects; tiredness leading to decline in physical activity, mistakes, forgetfulness, irritability, brain fog; poor mental health due to all long term effects of PKU, and the limited mental health facilities this country has results in no help; weight gain and fluctuation resulting in poor physical and mental health; epilepsy; tremors; sickness and vomiting; behavioural and learning difficulties; skin conditions… You have to ask yourself would YOU be happy with these long term effects knowing there is a life changing drug out there? I truly believe if there was more guidance, help and medication such as Kuvan, especially in the most crucial years of her life which are 16+, then she would have gone on to do amazing things.

Q7. My friend has always struggled with dental issues and as a child was referred to specialists in Guys Hospital for preventative treatment due to the high acidic content of her amino acid drinks, as well as high sugar and carbs of her diet. At the age of 16, the support from the specialists was removed, and she had to attend a regular NHS dentist. A dentist that does not have specialist knowledge of PKU. Her ongoing treatments have become extremely expensive for her, as well as feeling very insecure of her teeth. She also has to pay a £100 prescription cost per year for her food. A cost that will become very expensive and accumulate to huge costs when older. The food available on prescription is very basic, and yet is so needed and vital for her to follow as close to a "normal" diet as possible. One that is very evidently nothing like a persons without PKU. I can go out and eat as much chocolate and treats as I like, she cannot. I can enjoy my food without guilt and pressure, remembering to monitor and track it, she cannot. She has also had to fight to retain her regular prescriptions with her local GP, one that is also immoral and wrong. Her diet consists of a lot of vegan and plant based food - one that is very expensive for anybody to follow, let alone somebody with PKU that needs to follow a restricted diet so that their long-term effects are lessened.

Q8. I believe that NICE should definitely take into account family members and friends of those affected by PKU. My friends parents provided full support to my friend as a child. They cooked food, made her stick to the restricted diet, reminded her of when her drinks needed taking, supported her throughout her ups and downs. Acting essentially as carers was very draining, particularly when worrying constantly about their daughter. This worry did not go away once she turned 18, if anything it increased. As a parent has to once their child reaches a certain age, they had to step away and let her be independent. My friends husband has seen her ups and downs. Something that may seem minor to another such as Dr Pepper (her favourite drink) recipe changing to now include aspartame really made her down, and her husband. The restrictions she faces on a daily basis is hard for her, but also hard for her husband, family and friends.

Q9. There are many people with PKU who fall into the categories above. I do not think NICE has taken into account that gaining benefits is such a hard system and so financial support really can be limited. Financial support needed to have a good quality diet, to have regular dental care... I believe NICE have not taken into people with PKU at a disadvantage. This is negligent, and all to suit their goal to only provide children with Kuvan. To not take into account all factors irresponsible and careless. Kuvan would make such a huge difference in adults lives, and can be

argued it would make drastic changes for those in disadvantaged groups above. People with PKU are not numbers, people with PKU are people and should be treated as such, not discriminated against.

Q10. Finding out you are pregnant should be a happy time and celebrated, however, as a woman with PKU this would be terrifying. Knowing that your high phe levels could accidentally poison the child, have drastic effects on the mothers mental health, and the guilt you would feel is unthinkable. To constantly be aware of possible pregnancies in such a negative way in 2021, when there are drugs that would enable healthy and happy pregnancies is injust. Women should not be judged on their sexual freedom and desire to become pregnant, just as women should not be judged on becoming pregnant. Pregnancy is natural for women. Women with PKU who become pregnant have to think about all their options including abortion. This should not have to happen purely because they are at a disadvantage to those without PKU. No contraception is 100%.

Q11. I know that my friend is terrified of becoming pregnancy unexpectedly. This has been a worry since I have known her, and still is at the age of 27 when her diet is the best it has been for a long time. She is married, owns her own house, is employed full-time and yet this is such a heavy burden for her to carry constantly. The planning of a child 1-2 years before actually falling pregnant is not something anybody should have to worry about. The stress that comes with this would not be good for the mother or the baby. I am not aware, neither is my friend of the effects being pregnant with PKU, however since the age of 14 it has been stressed to her by dieticians and doctors the importance of NOT becoming pregnant. This has instilled a fear of becoming pregnant, or even discussing it openly. Kuvan would allow for women with PKU and their families to happily plan their pregnancies, without the fear and scaremongering that comes with it, as well as the shame. Contraception should also be taken into account. The pill is known to cause blood clots, mood swings and UTIs, as well as a number of issues with other forms of contraception. No contraception is 100%.

Q12. If preventing neurological damage to children of women with uncontrolled PKU was a priority than costs to parents and the NHS would lessen. If my friend had been diagnosed earlier than maybe her brain damage would be lessened or not have happened at all. Her high phe levels means she regularly has to pay for dental checkups, fillings, as well as prescription costs for her diet and purchasing plant based foods, all so she can live a normal life. Uncontrolled PKU should not be viewed as the act of a rebellious and irresponsible person, and as stated above NICE has not taken into account different groups of people who may have greater difficult controlling their PKU. PKU is a lifelong illness and disability, and should be treated with care and consideration, remembering that those with PKU are human beings. Kuvan would be life changing for those with PKU.

Q13. The stress, impact on mental and physical health, daily life, fulfilment and achievements, and the life of people with PKU has not been taken into account by NICE. It should not be such a simple view of cost. All factors should be taken into account to reach an educated, moral and just conclusion. A conclusion I believe that should include both children and adults being given access to Kuvan.

Respondent 100

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Allowing children to take Kuvan to age 18 would be totally detrimental to their ongoing health.

My son who is mid twenties was on diet TOTALLY till age 18 when he was basically pushed off diet by Alder Hey Children's Hospital. He (or I) did not want him to come off diet but we were ASSURED that the guidelines had changed and the PKU diet was no longer lifelong. We were told that the information given when my son was younger
(dementia type symptoms appearing around age of 40, off diet) was now no longer the case!! We were even given a letter (I can produce) from Alder Hey stating that being off diet would have no side effects at all, and that my son could apply for any of the armed services (something you are told at birth that PKU'ers cannot do).

My son was off diet for 5 terrible years. It took about 9 months for the first signs something was wrong to appear. My son began to develop signs of anger anxiety and depression. When he attended his new adult clinic in Salford Royal the consultant Prof Hendriksz simply said " How is your ANXIETY?"

My son immediately thought I had said something to this gentleman, when in actual fact neither of us had met him before. Prof Hendriksz then went on to tell us that my son would suffer whilst off diet and that the NHS are fully aware that those with PKU are suffering whilst off diet. My son took another three and a half years before he was literally not able to lift his head up, such was his ANXIETY AND DEPRESSION.
At this stage the GP had to intervene and my son asked to go back onto diet.

Can you imagine this???? Now not being able to eat what you want again, all down to NHS failings.

It took over a year for him to start to feel better. He is only allowed 10 grams of protein per day and he still has to have anti anxiety medication.

All people with this terrible condition are being let down by the NHS.

10 grams of protein when you are a child is an awful lot easier to deal with than 10 grams of protein as a sixteen stone man. Children are also cared for by their parents and food is prepared and given to them. As an adult trying to eat the correct amount of protein whilst trying to hold down a full time job and live a day to day life is very difficult. Can you imagine nipping into ASDA for a sandwich, Oh wait there is NOTHING you could pick up on the go like any other adult.

It makes no sense WHATSOEVER to say that there is no brain damage to adults, this is simply a LIE. This condition causes what I can only describe as FOGGY BRAIN.
My son struggles daily with life in general because of this terrible " unseen" condition.

This condition is no fault of anyone with PKU. It is inherited. They are born with it.
The NHS supports all the people who eat and drink themselves into illness - PKU'ers don't even get free prescriptions.

My son was actually one of those who did the trial for Kuvan many years ago and he was a responder. At the time of the trial Kuvan literally

doubled the amount of protein my son was allowed to eat. This made a massive difference to his young life.
It could make an even bigger difference as an adult.

Q3. I do not agree with NICE's view;There is total risk of brain damage in those who cannot keep their levels low enough.

Q4. PKU is a proven LIFELONG condition.

My son who is mid twenties was on diet TOTALLY till age 18 when he was basically pushed off diet by Alder Hey Children's Hospital. He (or I) did not want him to come off diet but we were ASSURED that the guidelines had changed and the PKU diet was no longer lifelong. We were told that the information given when my son was younger
(dementia type symptoms appearing around age of 40, off diet) was now no longer the case!! We were even given a letter (I can produce) from Alder Hey stating that being off diet would have no side effects at all, and that my son could apply for any of the armed services (something you are told at birth that PKU'ers cannot do).

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It could make an even bigger difference as an adult.

Q5. As per your comments above. PKU is like a vicious circle. Unless you have "perfect levels" you feel all of the above symptoms but you need to get you levels down - but because you have these symptoms nothing seems clear, it's very difficult to control levels when you don't feel clear headed.

Q6. Prof Hendriksz of Salford Royal simply told my son that PKU'ers do not often reach the heights in life that they would if they were given the correct treatment ie KUVAN.

The long term effects are terrible.

Q7. My son who is mid twenties was on diet TOTALLY till age 18 when he was basically pushed off diet by Alder Hey Children's Hospital. He (or I) did not want him to come off diet but we were ASSURED that the guidelines had changed and the PKU diet was no longer lifelong. We were told that the information given when my son was younger
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It could make an even bigger difference as an adult.

Q8. I am a Mum of a PKU'er. Although my son is mid twenties he still lives at home. I still have to check he has taken his supplements daily. I still bake his bread as he simply would not remember to bake the bread, or take the supplements, or take his medication. I have to prompt him to order his medical foods, or he would simply run out and have nothing suitable to eat. I live my life in constant "are his levels ok?" Although my sons levels (totally with family help) are reasonable, he does still have some minor memory issues and I can tell when his levels are not good as he becomes confused, moody and angry. If he had Kuvan and responded as he did as a teen, it would make a massive difference.

Q9. No! EVERYONE with PKU should be given Kuvan if they respond to it.

Q10. N/A PKU son. My knowledge of Maternal PKU is limited.

Q11. N/A

Q12. N/A

Q13. I feel that everyone who has PKU, a LIFELONG INHERITED condition, which is no fault of anyone who has PKU, should be given KUVAN if they respond to it.

Please realise that not everyone WILL respond to KUVAN, so it will not mean that everyone with PKU is costing money for Kuvan, but I feel strongly that EVERYONE deserves the chance to have a better life as a PKU'er.

My son cannot even go to a football match and eat a bag of chips on the way home, or have a few drinks as this is WAY over his allowance.

Please think on and imagine having to live this way for your whole life.

Thank you.

Respondent 101

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. After stopping the diet myself after puberty, I have found it very difficult to return to the diet later on in life for pregnancy and other health reasons. I find it too easy to stray from the prescription food and eat normal food. The fact that the diet is so very restrictive, I find it hard to stick to my 8 grams a protein per day which is all I can have.

Q3. I do not agree with NICE's view

Q4. My sister, who also has PKU has some damage to her brain (white matter). As a result, she has developed difficulties in walking due to the white matter on her brain causing communication difficulties between her brain and her leg. She now has long term use of a walking stick and for long distances she needs to use a wheelchair.

Q5. I experience all of the above side effects on a daily basis and find they are much worse when my Phe levels are high. The restrictive nature of the PKU diet causes me to suffer from severe depression, mood swings and extreme tiredness. I find this is because the foods that I can eat freely do not fill me up and give me the energy I need. I find it very difficult going to restaurants as the vegan and vegetarian foods on the menus are still very high in protein due to cheeses, soya products and creams.

Q6. No I do not agree with NICE's statement. The long term effects of my Phe levels have led to the various side effects listed above. Due to my brain fog, severe depression and forgetfulness, this I feel has severely hindered me in pursuing my career goals. The side effects of high Phe levels would hinder my ability to recall and retain important information.

Q7. Due to my depression and the other side effects mentioned above, I have undertaken counselling and also CBT and found that neither of these therapies are effective due to my fluctuating Phe levels. I have also seen a psychologist due to my worries regarding these side effects, they identified some issues with recalling and retaining information. I will continue seeing the psychologist at regular intervals and they will monitor me for the rest of my life.

Q8. Because of my severe depression, mood swings and tiredness my husband and 2 young children and general family life have been severely affected. My children feel they cannot talk to me or even approach me as a result of my mood swings. My constant tiredness means that we are rarely able to go out on day trips as a family, when we do manage to go out it is very difficult to find places to eat because of the restrictive nature of the PKU diet. My husband and I often have very bad arguments too. This is very distressing to both me AND them and we have come very close to parting ways as a result. My husband and children are very understanding and know that I am not able to control these horrible side effects. Despite this understanding, my family life can still be very challenging.

Q9. I personally feel that people from all walks of life that live with PKU should be offered Kuvan regardless of all the circumstances mentioned above. I especially feel it would benefit women who are on the pre-conception diet as to live on 3 to 5 grams of protein per day is extremely difficult. As a mother of 2 I know only too well how difficult this is and when I was on the Pre-conception diet I was severely underweight as a result (6 stone). This caused great concern to my consultants who considered hospitalisation throughout both my pregnancies.

Q10. I especially feel it would benefit women who are on the pre-conception diet as to live on 3 to 5 grams of protein per day is extremely difficult. As a mother of 2 I know only too well how difficult this is and when I was on the Pre-conception diet I was severely underweight as a result (6 stone). This caused great concern to my consultants who considered hospitalisation throughout both my pregnancies. Research has been concluded that women with high Phe levels during pregnancy have a increased risk of having a child with brain damage. My sister who also has PKU lost her child who had brain damage due to high Phe levels in her body during pregnancy. I urge NICE to make Kuvan available to everyone with PKU regardless of age and especially for women with PKU so they can have a family and not have to worry about the side effects of high Phe levels and their child's development.

Q11. Research has been concluded that women with high Phe levels during pregnancy have a increased risk of having a child with brain damage. My sister who also has PKU lost her unborn child who had brain damage due to high Phe levels in my sister's body during pregnancy. I urge NICE to make Kuvan available to everyone with PKU regardless of age and especially for women with PKU so they can have a family and not have to worry about the side effects of high Phe levels and their child's development. I would refer NICE to the following website link:

https://pubmed.ncbi.nlm.nih.gov/20123474/

There is a lot of information and research found online that detail the severe side effects of the restrictive PKU diet and also Maternal PKU.

Q12. I have no comments on this section at this time.

Q13. It is my view that NICE have NOT considered all of the evidence and research available. I feel that Kuvan is a vital medication for all patients that have PKU regardless of age, race, gender and abilities. I myself would be willing to trial Kuvan and I would like to be involved in any research or discussions that NICE wish to have with me.

Respondent 102

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. When they have gotten used to take Kuvan during their childhood whilst with caregivers you take it away from them when they reach adulthood and have more to contend with.

Q3. I do not agree with NICE's view

Q4. A close friend of mine is an adult and is struggling to hold down a full time job because of the effects of having high PHE levels when she struggles on her diet.

Q5. This has a major effect on quality of life on a daily basis, conversations, routines, self care. Everything is affected.

Q6. How can you put a cost on an adults life? High/low PhE levels will affect everyone differently. I definitely think high PhE levels in the past affects how you deal with life and the obstacles it brings.

Q7. A PKU diet is expensive. The specialty food that they have to have prescribed is vital to their daily living. Without a disability Pip payment this is very difficult to achieve as well as holding down a job to pay for it all.

Q8. Yes, PKU affects all the family members.

Q9. Everyone with PKU will have problems managing it no matter what background they come from.

Q10. Have they spoken to anyone who is of child baring age who get told from the time of puberty when they want to have children it will need to be managed very carefully, like before conception.

Q11. From the teenage years that’s all consultants will ask about when seeing patients for there 6months review.

Q12. Surely preventing is what needs to be done.

Q13. Without kuvan my close friend struggles with daily life. I have seen a dramatic change in her ability to cope with a full time job and self care whilst she has been on it. Taking this away from her would be devastating.

Respondent 103

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. My stepson has PKU. PKU has had an enormous detrimental effect on his mental health, his quality of life and his education.

His experience of transitioning from childcare to adult care services and going to university at age 18 was a traumatic time for him and for us as a family, due to the difficulties he faced managing his own medical appointments, blood tests, dietary therapy, mental health and university level

studies away from home for the first time in his life. He ended up dropping out of university and the resulting effect on his mental health meant he has been unable to adhere to the dietary therapy, hence a perpetual vicious circle of mental health issues and untreated PKU. He is now 22 years old.

The NICE proposal to offer children Kuvan up until the age of 18 only is dangerous and unacceptable for so many reasons, including:

- shows a complete lack of understanding and empathy of the patient's real life experience of the disease (forget the text books and medical papers - listen to actual patient voices)

- Such a significant change of medical therapy at age 18 would have a huge and potentially catastrophic effect on a person at an extremely difficult and important stage of their lives (doing A levels, starting university, start of working life, social and sexual relationships etc).

- Does not take into account the fact that PKU already has an impact on mental health (regardless of how well PHE levels are controlled) so increasing the risk of impacting their mental health even further is immoral and dangerous, particularly at time when mental health awareness is supposed to be improving in this country. It is NICE's duty to ensure our NHS provide therapies which prevent or reduce mental health issues, not be a cause of them.

- Disastrous decision to put in jeopardy the futures, quality of lives and health outcomes of a whole generation of young people with PKU, particularly when we failed previous generations of PKU sufferers by withdrawing them from diet when they were still children - something we now know, with the benefit of hindsight, was wrong. NICE cannot allow such mistakes to be made again and to fail another generation of PKU patients.

- Huge risk of these PKU patients treated in childhood with Kuvan becoming under- or untreated as adults due to the physical and psychological enormity of switching therapies at age 18. 18 year olds are at far greater risk of being under- or untreated due to the fact that this is an age where they don't have the benefit of hindsight, think they know everything, they like to push boundaries for their independence and are therefore likely to reject dietary therapy or follow it inadequately. They will not be happy with a second-rate treatment when they know a better treatment exists. They will rebel and who could blame them?

 - PKU patients deserve respect - you give them a medication that works for them and then take it away. It is just like a drug dealer giving you your first hit for free.

- the PKU "tastebuds" cannot just be "picked up" and learnt at age 18. A baby weaned on PKU foods usually develops a taste for foods that would be totally unacceptable to the palate of someone unused to PKU foods. I would gag if I was to eat some of the food we give to my stepson. They are not robots - they have senses and feelings and may not adjust to the dietary therapy. What then???

- the PKU dietary therapy "lifestyle" cannot just be taken up at age 18. To suddenly become "the one with the fussy diet" at age 18 is a surefire way of curtailing the social life and development of an 18 year old, encouraging social withdrawal .

- the PKU dietary therapy is not conducive to maintaining healthy weight due to the nature of the foods - this can lead to disordered eating or even starvation (in the case of my step-son). It would be irresponsible to put an 18 year old in the position of changing their whole diet at this age, when their appearance is very important to them, not to mention the issues that might be caused by the huge disruption to their gut biome system.

- Food choices are learnt by the brain and become automatic. Suddenly demanding the brain to forget choices and re-wire decision-making processes at the age of 18 is an unachievable goal.

- Patients on Kuvan have reported decreased anxiety levels, reduction in headaches and muscle pain, improved sleeping, improved moods, improved eating habits and less feelings of constant hunger. It is unethical to allow people with PKU to potentially feel these benefits of Kuvan during childhood and then expose them on their 18th birthday to higher risks of brain damage, increased anxiety levels, panic attacks, headaches, muscle pain, feeling of constant hunger, depression, gut issues, acid reflux and disordered eating, foggy brains and the like, not to mention a complete change of life-style.

- Children with PKU transition from childcare to adult care health services around the age of 18 - this is already an emotionally difficult period in the life of a PKU patient without the additional negative impact of a change of therapy.

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Q3. NICE's statements are contradictory

Q4. The human brain is more complex than any other known structure in the universe.

It is therefore inconceivable that NICE claim that there is absolutely no risk of irreversible brain damage to adults with PKU. How do you know when we, as humans, don't know what we don't yet know about the brain?

It is well documented that the brain does continue to develop well into our third decade and it is scientifically proven that neurological development is not complete at 18 years old (as acknowledged by NICE). Stopping KUVAN treatment at age 18 on the basis that over 18s are not susceptible to irreversible brain damage is a statement that will open NICE up to future legal action for medical negligence.

From our family experience, I can tell you what we know to be long-term damage my step-son has endured since he turned 18 from the effects of PKU-associated brain damage :

- Missing out on his full academic potential
- damage to teeth and oral health caused by the PKU diet and self-neglect during depressive episodes

- self-esteem issues
- self-confidence issues
- persistant general anxiety disorder and panic attacks
- depression
- body dysmorphia
- a full and healthy social life
- psychological damage from bullying for disability

Q5. My step-son is affected by the following symptoms: brain fog, forgetfulness, bouts of extreme fatigue and hyperactivity, painful headaches with changes to vision and "floaters", muscle pain/weakness, impulsive behaviours, hypersensitivity to noise levels, hypersensitivity to touch, low mood, lack of concentration, inability to focus, irrationality and defiance of authority, social withdrawal and feelings of irritability, aggression and anger.

In terms of how PKU affects his quality of life:

- inability to socialize/eat out spontaneously (at friends, family or in restaurants/bars)
- PKU is a time-consuming condition to manage (what with the dietary therapy, the notoriously difficult to cook PKU food products taking longer to cook and most stuff has to be prepared from scratch, the medical appointments, the blood testing, the procurement of PKU foods and supplements etc) and this means less time to dedicate to work, relationships and social life.
- Extreme fatigue can mean days off work/education/dropping out of social arrangements: my step-son often has the reputation of being "flakey" and his secondary school made no allowances for his condition - his behaviours were regarded as defiant , deliberate and unacceptable - meaning his secondary school years are a traumatic memory for him and for us, as parents.
- He wanted to do a gap year abroad and go travelling but that was impossible with PKU. eg PKU often limits life choices, including career choices - you cannot join the armed forces if you have PKU as you may be posted abroad where they cannot guarantee to meet the dietary therapy requirements.
- Coping with anxiety and panic attacks
- Low confidence and self esteem
- Facing daily discrimination for what is essentially a hidden disability
- Shame, humiliation and a sense of failure for having a disability due to his PKU
- Avoids situations where there might be confrontation or attention on him.

How PKU affects our quality of life as a family:

- Personal stress and anxiety, particularly when the depressive episodes are frighteningly bad
- My wife being constructively dismissed due to asking for flexible working conditions to accommodate being home in time for evening meals
- My wife unable to hold down a full time job/loss of income due to her carer role for PKU son.
- Always watching what we eat as a family and conscious/guilty of eating foods that he cant. Hiding foods from him that might tempt him.

Q6. Of course high PHE levels in the past affects future health and life experiences. As mentioned above, the results of high PHE levels have already shaped my step-son's young adult-hood and continue to do so.

Due to the effects of high PHE levels, my stepson hasn't achieved his full academic potential and therefore, he has to work harder than his peers to achieve his career goals.

As for his health, we have no idea ----and more importantly, nor does NICE -----of long term effects on future health due to past high PHE levels. We don't know how it affects white matter and what the significance of the white matters changes, experienced by PKU patients, will be now, let alone in old age. We don't know what the link is and whether there is increased risk of PKU patients developing brain diseases, like Alzheimers, Lewy Bodies Disease and other forms of dementia.

In my view, NICE has a duty of care to ensure that the NHS can do all it can to ensure that mistakes aren't made, like we made in the past taking kids off diet at 8 ..... we must be cautious where the brain is concerned and not make unsubstantiated assumptions that there will categorically be no risk of brain damage to the brain of a PKU patient after they turn 18 years of age! We do not know this.

Q7. Yes - mental health care - sadly lacking in the UK . CAMHS was bad , but access to adult mental health care services in the UK is abysmal. There should be mental health specialists as part of each and every PKU metabolic clinic throughout the country - not just someone in another department who can be called upon every now again.

- Access to adult mental health care services requires that you be on the verge on suicide before any meaningful help is provided.

- Our family has paid out thousands of pounds in private mental health care and counselling services since my stepson turned 18 because the NHS does not provide this.

- There are no provisions within the NICE draft Guidance on Kuvan for the NHS to provide the tailored mental health care services for PKU patients that are already required, let alone the requirements that 18 years will have if the draft is approved.

- The demand on mental health care services is expected to increase massively due to the Covid pandemic, leaving people with PKU even further behind in the pecking order.

Q8. The impact of caring for a child with PKU is huge. It is documented and it is recognised that that burden disproportionately affects women. It is therefore sexually discriminatory under the Equality Act 2010 if you do not consider the full impact (financial, social an psychological) of carer disutility associated with with caring for a PKU sufferer.

Parents deserve peace of mind about their child's condition whether they are 22 months or 22 years.

Q9. No!

This guidance is blatantly discriminatory with regards to sex, age, disability and pregnancy and maternity.

The NHS is required to have regard to the need to eliminate inequalities of provision of care under section 13G of the National Health Service Act 2006 (NHSA) and is also subject to Section 147 - Public Sector Equality Duty of the Equality Act 2010, to ensure that the human rights and equal access to heathcare is respected.

The European Guidelines for the Treatment of PKU (EGTPKU) stipulates that PKU patients of all ages require of treatment for life. It is therefore discriminatory against age and goes against the recommendations of the EGTPKU to restrict access to Kuvan to PKU patients under 18 years and refuse access to the only other treatment for PKU available in the UK, to PKU patients over the age of 18.

PKU women planning a family or pregnant suffer unspeakable stress and strain during the pre-conception and ante natal periods, as well as post-natal, coping with their own health plus concern for their baby and the dreadful, horrific consequences of high PHE levels. It is discriminatory against maternity and pregnancy to not offer an alternative treatment to PKU adult females over the age of 18 who cannot adhere to diet or for whom KUVAN would improve quality of life during their child-bearing experience.

It is discriminatory against disability not to offer an alternative treatment to diet to adults with PKU because they are struggle with or unable to manage the dietary treatment because of their disability. Many of whom have a disability because the NHS does not provide adequate alternative treatments to PKU sufferers who are disabled because of untreated or under-treated PKU or were told to come off diet too early in the 60/70/80s.

It is discriminatory against gender to not consider the quality of life of the carers of people with PKU, which is a life-long commitment and a heavy burden of care which, as has been shown in studies, disproportionately affect women - given that it mostly mothers who give up their career and ability to provide income for the family in order to care for their PKU child.

Q10. The answer to this is clear cut. NICE should make the recommendation to offer PKU woman the chance to see if they respond to Kuvan. If so, they should be able to take Kuvan as soon as they are planning for a baby in order to eliminate the need for the dreadful dietary therapy pre-conception, ante and post-natal. The psychological burden on PKU women who wish to have a child is almost unbearable - it rips relationships apart, it causes women to chose to remain childless, it results in post-natal trauma and depression. Holding back a treatment which could prevent this trauma is unethical.

Q11. We have family friend with PKU who's marriage broke down within a year due to the stresses and strains of her pre-conception diet difficulties. She is so traumatized by the strictness of the diet and its incompatibility with everyday life, that she won't do it again no matter how much she wants to have children more than anything in the world.

Q12. *[no response given to this question]*

Q13. The Department of Health and Social Care recently issued a 5 Year Strategy on Rare Diseases which made promises to people with rare diseases like PKU. This document states:

"...we aim to ensure no one gets left behind just because they have a rare disease"

“We want to put the patients’ needs first.”

“The UK will take action... by empowering those affected by rare diseases”

“The care pathway will include.....the development of seamless pathways for transition, from childhood to adolescence, and on to adulthood and older age”

NICE need to take into consideration the promises and commitments the Government has made to people with rare diseases like PKU as currently, the Draft Guidance on Kuvan appears to pay no heed to this Strategy document and its contents.

We urge you to amend the Draft Guidance to ensure that PKU patients of all ages are offered fair and equal access to Kuvan, regardless of their age and that the dosing guidance is per the manufacturer instructions so that the dose is sufficient for adults too.

Respondent 104

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I believe this is extremely detrimental to a child/ young adult and is counter intuitive to an individual's ability to stay compliant with what is an impossible to follow diet especially in the teenage years and adulthood. I have a daughter with Pku, she's 20. I am an educational psychologist by trade and knew with my job the teenage years would be a challenge. They were far worse than I imagined, we had almost 3 years of hell to be frank. Our daughter is on 4g of protein a day. She used to say wouldn't it be good if I got to 9 with kuvan.... Friends recall me saying as a baby that it would be hard as a teenager. However, imagine being on 9g protein and at 18, kuvan is removed and you go back to 4g. It is very ethically unprofessional and children growing up with PKU have a reduced access to whatever they have eaten as they turn 18. It is an unforgivable decision and will cause both physiological and psychological difficulties. Adolescence is a tough period for many, as evident with those requiring mental health support in childhood (CAMHS referrals are huge and I see that through work) and the teenage years. A serious metabolic condition adds to that. Giving a drug that supports dietary compliance to remove it is unethical and definitely in no-ones best interests. The diet is massive in restrictive and means my daughter eats just the same 3 meals a day and she rotates her lunch and evening

meals. There is no pleasure in eating; she views it as a job/ duty that happens to keep her alive. That's how restrictive it is. She was delighted after cancelling her driving test that she could celebrate with a bag of walkers crisps. How many 20 year olds see that as celebratory. A small bag of crisps is 2.5 G protein compared to a bag of quavers at 0.4g. Kids on kuvan who may be able to have a weetabix (2g protein fir one) or crisps will have to stop this at 18. This coincides with perhaps university and managing food/ budgets etc and would be extremely dangerous and difficult for a young adult to have to reduce what they eat and a time that comes with challenges as well as opportunities.

Q3. I do not agree with NICE's view

Q4. Our daughter went off diet outside the family home for almost 3 years, this affected her hugely and she has been left with mild neurological damage that we can see as a consequence. She has a small hand tremor which even how worsens with high blood levels. We cannot see what brain damage may have occurred inside her head. Whoever is reading this (and thank you for doing so), you have phe blood levels between 40 and 90. For a protracted almost 3 years our daughter's levels were around 1200/1500, imagine the toxicity to the brain. This was due to buying cookies after school, eating pizzas at parties (as everyone else was having them) and struggling with the necessary protein substitute causing tummy upsets. All forbidden fruits that most teenagers have and which are not allowed for thise with PKU. Much is well documented about the relationship with anxiety/ depression and of course the chemicals in the brain. We believe our daughter struggled with these as a direct consequence of eating what she shouldn't. She required CAMHS support which was as sorely and sadly lacking as I see routinely with work, as the calibre is not what it once was even a decade ago. I have been an educational psychologist for 29 years now. She eventually needed sertraline for anxiety and when at almost 18 she decided to return to the 4g protein a day / PKU regime, she eventually did not need the sertraline but I have no doubt that the inherent difficulties in complying to 4g a day is impossible and suspect she's having to try and manage on perhaps 7g. She eats avocado on low protein bread for breakfast, low protein pasta and home made tomato sauce and sweet potato curry with rice. Plenty of fruit of course. She rotates those two meals. Recently she has used some vegan cheese as well. She needs to eat in this way as otherwise she will revisit the neurological damage affecting fine motor coordination and anxiety/ depression. This was a sad sight for us as parents when she began to develop an eating disorder at the age of 15/6 and we had lost our cheerful happy child. I really believe so many adults are struggling to adhere to the rigours if the regime and when life has its own additional challenges as it does at times then adults without kuvan are going to struggle, in every way.

Q5. Our daughter's demise into a three year hell was characterised by all of these. She apologised for being a bad daughter.....she was tired and irritable. She looked awful and her eyes seemed vacant. She was awake at night. At sixth form she struggled, started to skip lessons and school forced her to drop an A level and were unsympathetic. She has admitted that having driving lessons last year was stressful as she can't concentrate and that's with her trying to manage her diet well in the last 3 years as she's almost 21 now. It makes you wonder how many adults are struggling and we can tell now when our daughter's levels are high. You see a demeanour change. It's maybe like having PMT all the time. It's a vicious circle too as you are tired, can't sleep, can't be bothered to cook yet are tired/ hungry. In retrospect I think our daughter feels considerable guilt and she won't talk about this period though did admit to making herself sick and it was a recovered anorexic who told her mum about our daughter who then contacted the school. It was a terrifying period and with my work I know it's one if the few mental health needs where treatment in the last century has not improved outcomes. We were fearful to see our daughter struggle in this way and also struggled to get the right support for her. I guess when you can't control things and you have to have control the PKU regime, an eating disorder is perhaps not unexpected. I also feel that hunger drove this too because you can't just grab something, like others can and again to remove kuvan at 18 will cause all of these problems cited in this section. I had met two children with the condition through work and one had concentration issues even as a child and the family was chaotic which may have affected the child's experience with PKU.

Q6. I appreciate there are challenges in quantitative research but I feel strongly that it's false economy when calculating costs. There are additional and different costs due to the impact of PKU. As a parent you control your child's eating phenomenally well. You remember the Thursday at 9 days old when you had the phone call about the diagnosis and that this perfect baby has something really serious. You know you can do it as you want the best outcome for your child. You also have the naivety as a parent that all your PKU parenting will rub off and I thought my daughter would go off the rails maybe at uni and away from parental eyes who scrutinise everything that goes in their mouth. You need to! I didn't anticipate the severity of what we went through and yet I now know how common her experience is and especially in adults trying to lead busy lives, hold down jobs etc. I have no doubt that my daughter's quality of life would improve were she able to eat more ordinary food and so it is vital that NICE recognises that kuvan AND also other treatments hold out hope fir a more ordinary life. It is enormously time consuming to care for a child with PKU and I didn't go back to work full time until she was about 12. I sleet a day a week cooking and for adults with PKU how do they find this time. Associated costs on the NHS with mental health difficulties are inestimable but also missed time working and to the economy plus as yet unfolding medical issues that will cost NHS time due to the impact on the body of running high blood levels. So cost effectiveness needs to be about the bigger picture ideally.

Q7. Sorry I have gone into this above. My daughter has had some gastric issues previously but is on a different substitute now. I do worry about her ability to cope and juggle as she's older when she has a job and/ or family as so little time is available. No doubt she will be eating those same three meals. It's very challenging fir children and their parents to see their children grow up with such restrictions and there is pain and anguish that everyone has. Even simple things like you can't have an ice cream at the seaside because you don't know what's in it or maybe it's 3G of protein so on 4 you then can't eat much else that day. We did use to have more treats on holiday but sometimes that caused tension if parents have a different vuew on it. Just a week ago today for mother's day I went to town to meet my daughter as she's now at university, PKU has meant it's delayed her opportunities but at 20 she started at Newcastle uni where we live. We often get a take out from two places she likes and have a walk in the city park. She couldn't have anything to eat she said as she felt her levels were high. She looked unwell and maybe she'd eaten things she shouldn't with her friends but 4g a day is really not easy to stick to.... An egg is 7, a slice of bread is maybe 6/7, a biscuit 2/3, a magnum about 5, a teaspoon baked beans is one G protein. Have a look at some food packaging next time you are out. It's vvvvv tricky. Some Ainsley Harriet packet soups are about one g but my daughter complains she dies NT want processed foods but also fruit and veg aren't filling plus they too need measuring so she can't have roast potatoes and peas on a meat free Sunday lunch as both potatoes and peas need weighing. 4g means you can't. Usually she has about her 3/4g allowance in mash. Potatoes need weighing and maybe an average chipshop chips portion is about 8 exchanges. She can't have sweet corn and peas at the same meal either as they all need weighing. We always carried some food on our person when little as you can be caught out with people offering chocolate (not permitted fir our daughter as too much protein). There's definitely associated NHS costs fir PKU in adulthood. Please reconsider kuvan fir adults.

Q8. I definitely earned less due to PKU but I do have a professional salary that allowed me to have a full day cooking and baking each week and reduce my hours. Then she liked those special cakes. Now she won't entertain them because of this. There's hidden responsibilities that people never appreciate like the extensive liaison that goes into a child attending a party. So of course chicken nuggets and chips ain't possible bar the

chips. If it's a party with food put out we would take something similar to place on out daughter's plate plus watching her like a hawk to check she wouldn't eat anything she shouldn't or that she's offered it by another adult who might be unaware. When older parties in restaurants meant checking if the restaurant would be prepared to cook the low protein (not a given) or me taking a home made pizza base and special cheese ahead to the restaurant. Once pasta was done and given when others had a starter and when the mains came she just sat there! You go to parties and you can't eat the cake. One year my daughter said she wanted an Asda cake so it was normal and then she just wouldn't have it. It's definitely a challenge be to do PKU well and there are both time and associated psychological costs. Fir her 18th she wanted a pizza in a restaurant. She chose an ordinary pizza (25g protein) in Edinburgh and then we had an argument over it and she didn't like it that much and then felt crap next day plus very guilty. Not a nice birthday and people don't have a clue. If you go on a long haul flight, we take loads of food on and then you have to liaise or they don't do it as fair enough it's complicated. We often get a meat, a veggie and a began and swap what's on. Holidays can be a challenge too and we once took a portable tiny fridge as hand luggage.

Q9. I have no doubt that these people will have additional challenges. As well as understanding the intrinsic condition, people need to be able to read packaging and contents. They need to do the maths as constantly you are calculating amounts in packets, say three sweets is equivalent to 0.9g protein. The implications fir outcomes for children of people with these different needs will absolutely impact on that child's development, to the point that safeguarding may need triggering. I am of the view that NICE doesn't really understand the condition and unfortunately as is evident at the annual PKU conference that bit all consultants nationally have a good insight. As with many things it's lived experience that provides insight and yet we know that kuvan helps many people have a better quality of life which in turn supports dietary compliance and reduces NHS costs. I absolutely believe it to be immoral and unethical to give kuvan to children and to withdraw it. It could have devastating consequences.

Q10. Kuvan is critical to a woman's ability to prepare and maintain a safe pregnancy. Our daughter has said she would like a baby in the future. The reality is that to be given the go ahead to conceive you have to have very very low phe bloods and for our daughter that ,st have to be one or less grams of protein. Impossible and you have to maintain this fir a while to start trying and then it may take a while to conceive. Imagine if as a woman reading this you feel rubbish and sick in that first trimester yet you can't eat what you want/ fancy, you MUST absolutely have to take the three protein substitutes daily as they are critical to managing blood levels. A rise in bloods can and will affect the baby's development. If you are sick you need to have those protein substitute drinks again, you can imagine. It can be a torturous process. Kuvan fir our daughter may mean she can have her four grams of protein instead of zero. I absolutely think it's discriminatory to not license kuvan for women. Many choose against having kids and that's such a shame or after one child think they can't repeat the process. It's very important kuvan is availale pre and during pregnancy. As you note above many things are indeed challenging to model and hopefully peoples' vignettes and examples shared here will help you. Imagine if what I am talking about here were your wife, sister or daughter?

Q11. My understanding is that it's a nightmare and a dreadful responsibility psychologically that you have so much burden desperately following the PKU regime and with hormonal emotionality the challenges this brings.

Q12. This is important! I see children in special schools who are often adopted children whose mothers misused drugs and alcohol and they have foetal alcohol syndrome. We know a controlled pregnancy produces a good outcome and there is much research highlighting the impact of uncontrolled levels. Why increase the potential special school population when a drug can promote a safer pregnancy. A baby with additional needs later becomes a child and adult with additional needs. This will cost more to the NHS in the long term.

Q13. *[no response given to this question]*

Respondent 105

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Allowing children to take Kuvan is most definitely a step in the right direction. Growing up with a strict PKU diet was incredibly challenging. School life can be challenging at the best of times, but having to manage such a strict diet at the same time was often a step too far and my control during this time was very poor. I welcome the use of Kuvan to children. However, stopping treatment at such a crucial time would be extremely detrimental. At the age of 18 young people may be looking at starting higher education, work or perhaps leaving home for the first time. A very important and challenging time, even for those who do not have PKU. To expect someone to take on all the challenges of maintaining a PKU diet when they have little or no experience of doing so is an unacceptable expectation. Particularly when there is a medication that can treat PKU so effectively in many cases.

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. *[no response given to this question]*

Q6. *[no response given to this question]*

Q7. *[no response given to this question]*

Q8. *[no response given to this question]*

Q9. Kuvan is estimated to work in at least 30% of patients. Not every PKU patient in these groups will be responders for Kuvan. Carrying out genetic testing or trialing Kuvan in these patients will determine who does respond. So a "cost effective" solution would be to find out who responds. It won't be 100% of patients, but it would be life changing for those that do. Testing, trialing and issuing Kuvan to the responders of the above groups of people should be a priority.

Q10. Kuvan should be available to all Women following a pre-conception diet and those who are pregnant.

Q11. Whilst keeping phenylalanine levels below 600umol/L is a challenge, following the pre-conception diet is extremely challenging. It is essential that phenylalanine levels are kept within a much lower target range.

I have been on the pre-conception diet for 5 years now. I have suffered 6 miscarriages and I have been through 3 rounds of IVF since then

(funded privately). That means that I have been on no more that 5g natural protein a day for 5 years to try and have a healthy pregnancy. My phenylalanine levels are extremely hard to control along side my IVF medication, hormone changes and fluctuations in weight caused by my IVF medications (these all cause uncontrollable instabilities in phenylalanine levels). I try my absolute best to maintain my levels by diet. At numerous times during my IVF treatment I had to take 4 injections and 122 tablets daily to include my PKU supplement. I have been fighting side effects like extreme fatigue, headaches and nausea to prep my food. This has to be done as there is simply no other option. I have had to leave my job to manage my PKU alongside IVF which adds financial pressure when we have no choice but to fund our fertility treatment privately.

Each time I have become pregnant, my levels have shot up and I have had to go straight to zero grams of natural protein and increase my amino acid supplement to over 100 tablets a day. That is an incredibly difficult diet to manage. I have good communication with my dietetic team several times a week to ensure that I am doing everything I can. Having access to Kuvan would make this extremely difficult journey a lot easier. I am trying to bring my levels down knowing that the medication that I will be given as part of my IVF treatment in preparation for an embryo transfer will send my phenylalanine levels up again. It is almost impossible to keep them steady. I know that I will be back on zero grams of natural protein again very soon.

Q12. In not including this I would assume you expect all women to follow at least a PKU diet, if not the pre-conception diet. Make it easier for women to keep low levels by providing them with access to Kuvan. However, pregnant women with uncontrolled PKU should be a priority for this treatment. It is essential they get levels low and it would be extremely difficult to do that if they are not used to following such a strict diet. Much like if you took Kuvan away from children at the age of 18.

Q13. *[no response given to this question]*

Respondent 106

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I am a parent of a 20 year old daughter with Classic (and severe) PKU and based on this experience I find the proposal a tragic mistake that appears to show a total lack of understanding of the nature and the consequences of this condition. The condition, especially so for the severe suffers, is such that it affects many aspects of the suffer's, and their family's, life. The only current way to try and mitigate the potentially dire consequences of this condition is to employ an extremely restricted diet along with additional supplements that are themselves fairly unpalatable. To consider this 'special diet' as an effective solution is actually also to miss-understand the 'diet' and the consequences of living with PKU. Firstly, the outcomes for individuals are, sadly, not as good as they could be in terms of long term mental health, happiness and educational and individual attainment. Secondly the diet itself is almost impossible to live with for many people. Therefore, to see an individual grow up with a treatment such as Kuvan with its benefits in terms of the dietary freedom, mental health and general well been and then see it withdrawn at 18 and have to fall back solely on dietary treatment will be both tragic and often impossible and have very significant adverse outcomes. And if those people making this decision think that this is an overstatement then I suggest that they try my daughters diet based on 4g of protein per day for one to two weeks and see for themselves.

Q3. I do not agree with NICE's view;NICE's statements are contradictory;I would ask how NICE know what the true long term risks are for a condition that has only really been treated for around 50 years and has such a small cohort of suffers. Indeed I would also ask what NICE mean by brain damage in adults? This can mean many things and needs to consider all aspects of the functioning of the individual including already established problem areas for PKU suffers of concentration, reaction to stress and heightened anxiety and reduction in IQ.

Q4. Our daughter suffers from heightened stress and anxiety - Sometimes debilitatingly so. This is true for many people across society but it also an accepted fact within the scientific/PKU community that there is a much heightened level of this in PKU suffers.

Q5. I think that these comments sum up many of the symptoms of PKU; We have certainly seen all these in our daughter (and reported by her) at times. However, they should also include heightened, and potentially debilitating, anxiety and also problems with the nervous system which are known to manifest themselves in mild tremors for many relatively early in life but for which the long term prognosis is as yet unknown. It also is worth noting that the severity of these symptoms are often proportional to the lack of control in the diet and that this can become a negative cycle that is very difficult to break out when a problem occurs. To put this into perspective, we had several instances following typical child illnesses - and illness completely upsets the metabolism - when our young and generally pleasant and placid daughter acted like she was "possessed and a character out of the Exorcist". It is also worth noting that quality of life for most people includes positive aspects around food, family meals, celebrations and eating out in general but for most PKU suffers, to be clear, this is not the case and all of these can become negative experiences sadly.

Q6. I completely disagree and again think that this shows a lack of understanding of the consequences of this condition. Firstly, as previously stated I would challenge NICE to try our daughter's PKU diet for a week including eating out with family and friends to see how difficult it is to comply and therefore control the phe levels. Then I would ask them to consider the established "Symptoms and quality of life" detailed in section 3 above as well as the proven problems around reduced executive functioning. All of which could seriously effect individuals ability to hold down a job/career and even maintain and devlop friendships. I would also point out that the psychological and/or physical damage done by all these factors over an extended period cannot be ignored even if future control could be guaranteed - Thats not how the human mind etc function.

Q7. As yet the true long term effects of this condition are unknown because we do not have enough data for a complete age range for the PKU community. Therefore, the true future costs are unknown. What we do know is that the PKU community suffer from heightened anxiety and depression. These will obviously have health care costs on top of the individual's sad (or worse) experience. Indeed, who knows how many additional PKU suffers will go on to self harm, or worse, as a result of this condition and its treatment. We do know also that PKU suffers have issues around hand tremors and some motor skills. None of which are likely to get better with age and therefore the true cost of this condition may not be known for some more years.

Q8. The effect of PKU on families life is in our experience very significant and for the most part negative. The management of the diet/condition is certainly easier with babies/younger children but even then, if you want to make the diet as healthy and interesting as possible for the suffer you need to spend a lot of time and effort making special low protein foods/meals which cannot be bought in the shops. As they grown up this becomes more and more difficult for all concerned. Meal times can become a battle because the suffer cant have what the want or what every

other family member can. Eating out is often a nightmare with very little, if anything, suitable on the menu. Children's parties and school dinners are also a nightmare for the child as they just emphasize that the child is different which is not what most children long to be, and this too can have a significant effect on mental health and self esteem. Travel and holidays nicely encapsulate all these issues and add language difficulties and boarder controls for dietary supplements and low protein foods into the mix. So this condition certainly affects the whole family, the family dynamics and the family happiness.

Q9. I have no first hand experience of most of these groups but based on my own family experience, which was hard enough, I can only imagine the added hardship that some or all of these disadvantaged groups might suffer. Certainly, copying with this condition as a middleclass family (with all the benefits that that entails), with 2 parents, supportive extended family and friends was hard enough even with only the one child. With other children, lack of family support, or for single parent families (no judgment on this point by the way) these hardship would be much more. Additionally, it should be noted that to make this diet as healthy and interesting as possible, requires considerable extra time and money to get low protein foods bought and prepared and this is not something that every family may be able to do. One group that is clearly disadvantaged, with potentially dire consequences, are women with PKU who need to control phe levels prior to conception to avoid damage to the unborn baby. THIS NEEDS NO EXPLANATION and for all women, maybe especially women like my daughter who have severe PKU, this may make it impossible for these women to have the pregnancy they should reasonably expect in a civil developed society like ours. It also certainly means that some children will be either aborted or born with brain damage that would otherwise have been avoided. Whilst I have to point out the costs of this to NICE I think that the human tragedy is clearly the more important point to consider.

Q10. I believe that NICE need to engage with current and future mothers to determine their experiences and views. On the science, I think that this is one area where NICE should take a lead from the professionals involved in PKU day in and day out and especially those involved management of maternal PKU. I think that they then may want to apply a precautionary principle in this particular area recognizing that this is still a relatively small population and think that they need to check the data again because I am absolutely convinced that the benefits to the unborn child of enhanced phe levels are clearly established and accepted

Q11. I would refer to my previous answers and also to all the current and future mothers, and the maternal PKU professionals out there that I am sure are answering this questionnaire now

Q12. An unacceptable approach and oversight on both a purely financial basis and also, most importantly, because of the known consequences for the unborn child and their family.

Q13. It is sometimes said that "PKU is a diet for life". It is much more than that for the suffer and their family. The consequences of even a well controlled diet for the individual and their family are many and well documented in terms of their physical and mental health and general happiness and life chances. They are also consequences that have life time effects - the extent of which is still not fully known. So any treatment that gives more flexibility in the diet and helps control phe levels will make a significant contribution to the health and happiness of these suffers, their families and ultimately to society. This is especially true for younger suffers but it also applies to adults who still have to contend with this condition. Therefore to treat younger people is certainly good but to withdraw it for adults is wrong and be catastrophic for many individuals and to be honest inhumane to may - Again I challenge the members of NICE to try the severest form of this 'diet' even for a week before they make any final decisions. Last, but not least, the decision to withdrawn this as a potential tool for planning and managing a pregnancy's is particularly distressing and again inhumane.

Respondent 107

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. My young neighbour has PKU and I have seen first hand how this rare disease affects him, how it has affected his education and his ability to attend university. It has been devasting - not only, through no fault of his own, is he unable to adhere to the PKU dietary therapy (a complicated, time-consuming, onerous, unpalatable, restrictive treatment which seems to be completely incompatible with a normal life) but there is no alternative treatment for him.

As a former lecturer for university courses, I am well aware that when an 18 year leaves home for the first time to go to university, it is an extremely steep learning curve for them. For an 18 year old with PKU, this learning curve is multiplied : e.g. in addition to leaving home, shopping for themselves, registering with a new GP, studying independently at tertiary level, managing their finances, household chores, personal admin and bills for the first time, an 18 years old with PKU has the additional burden of managing their dietary therapy alone for the first time in their life, cooking the notoriously difficult PKU foods, arranging their multiple and regular pharmacy orders/collections & deliveries, sorting out wrong or missing orders, fighting their own corner with GP, receptionists & pharmacists just to get their food, taking their own blood tests and posting them to the lab, working out how they will socialise with their peers and not compromise their PHE levels, working out what drinks they can safely drink at the Student Union Bar, remembering to attend their hospital appointments and keeping on top of their mental health.

And what if they want to go on a gap year or study abroad ? It would be an impossible option for them with PKU.

Clearly, for someone with PKU switching therapies from a successful pharmaceutical treatment to a complex dietary treatment with no guarantee of success at the age of 18 and taking away their life options would be catastrophic for a whole generation of young people with PKU. Not to mention the huge strain this would put on whole families, dealing with the mental health fall out.

I have two teenage boys age 14 and 15 and if either of them had PKU and were offered Kuvan, knowing it would be stopped on their 18th birthday, we would most definitely chose to not start it.

Q3. NICE's statements are contradictory

Q4. I do not agree that there is no risk of long-term brain damage in adults.

The human brain is one of the most complex structures known to man. In my opinion, NICE cannot make a categorical statement that there is no risk of irreversible brain damage beyond the age of 18 years. Indeed, it is now known that the human brain may not be fully formed until the age of 25 years, and perhaps as late as 30 years old. The brain also continually develops throughout our lives. It is unthinkable that NICE is

even considering stopping a treatment that prevents brain damage at age 18 when it is fully recognised that the brain continues to develop beyond that age.

Secondly, given that NICE is fully aware that there are currently many PKU patients over the age of 18 who, due to inability or disability to adhere to dietary therapy, are currently under- or untreated, it is unethical and immoral if you allow these patients to spend any length of time with damage to their brains, reversible or otherwise, when there is an option of an alternative treatment. The NHS has a public duty of care to ensure that all patients with PKU are given fair and equal access to healthcare, and this is particularly important, when it concerns a rare disease for which there is little choice of treatment options. If one doesn't work, they must be allowed to try the other.

Q5. It is well documented that whether a person with PKU is able or unable to adhere to the current dietary therapy, they can experience terrible symptoms such as ‘brain fog’, forgetfulness, fatigue, confusion, low mood and feelings of irritability, lack of focus, inability to focus, as well as aggression, restlessness, headaches and irrational thoughts and behaviours.

It is only logical that this has an effect on the quality of lives of the patients and their families! It affects their ability to study, to run a home, to care for their dependents, to hold down a job and to look after themselves.

Q6. Past high phe levels clearly can affect your future health or life experiences. My neighbour has had PKU-related mental health issues for several years now. These are the types of problems that do not disappear over night, cost thousands of pounds in therapy and affects one's ability to study, to run a home, to care for dependents, to hold down a job and to take care of one's own health properly. This can shape a person's whole life - you can't get back the lost years.

Q7. The costs of mental health care can be high for PKU patients, much of which is not available on the NHS. Private therapies are costly and not an option for many, particularly those who have are struggling financially and are unable to work full-time because of PKU-related brain damage symptoms (as described above).

Q8. NICE should take into account the impact of PKU on other family members and especially, the carer disutility element.

In this regard, women are disproportionally affected by the care burden of family members with PKU and often it is mothers who give up their careers and ability to earn income in order to manage the huge burden of having a child with PKU. [The personal burden for caregivers of children with phenylketonuria: A cross-sectional study investigating time burden and costs in the UK. Mol Genet Metab Rep. 2016 Aug 28;9:1-5. McDonald A et al].

This disutility does not stop when a family member turns 18 years old for two reasons:

- family members continue to provide care beyond the age of 18, especially whilst living under the same roof or providing support whilst at university (unless you are from a wealthy background, it is very unlikely these days for an 18 year old to leave home permanently and have their own home)

- women who have been out of the workplace for many years caring for their PKU child have difficulty getting back into similar level jobs they held previously. This is particularly the case for people in professions which require up-to-date knowledge and Continuous Professional Development (for example, the legal profession). They may have to take lower ranking, lower paid jobs or may never be able to get back into their original profession and have to retrain. Having a child with PKU affects your career well beyond them turning 18.

Q9. NO.

The draft Guidance discriminates against age, gender, disability, and pregnancy and maternity and is totally inethical.

Under section 13G of the National Health Service Act 2006 (NHSA) and Section 147 - Public Sector Equality Duty of the Equality Act 2010, the NHS is required to provide fair and equal access to healthcare.

The European Guidelines for the Treatment of PKU (EGTPKU) makes it clear that PKU requires treatment for life. It is therefore discriminatory to only offer a PKU drug to people with PKU under the age of 18, particularly when the only other available PKU treatment in the UK is not always suitable for or adhered to by all patients. The NHS is fully aware that many adults PKUs in the UK are currently under- or untreated due to the fact that they cannot adhere to the dietary therapy. These patients are offered no support and no alternative. Now we have Kuvan, it would be discriminatory (and unethical) to not offer them access to it because of their age.

PKU women planning a family or pregnant suffer unspeakable stress and strain during the pre-conception and ante natal periods, as well as post-natal, coping with their own health plus concern for their baby and the dreadful, horrific consequences of PKU Maternal Syndrome. It is discriminatory against maternity and pregnancy to not offer an alternative treatment to PKU adult females over the age of 18 who cannot adhere to diet or for whom KUVAN would improve quality of life during their child-bearing experience.

It is discriminatory against disability not to offer an alternative treatment to diet to adults with PKU because they are struggle with or unable to manage the dietary treatment because of their disability, whether those disabilities are caused by under- or untreated PKU (eg mental health issues) or other disabilities (such as learning difficulties - especially if those disabilities were caused by our NHS erroneously taking them off dietary therapy from a young age whilst their brain was still growing).

It is discriminatory against gender to not consider the quality of life and disutility of the carers of people with PKU, which is a life-long committment and an heavy burden of care which, as has been shown in studies, mainly falls on the mother, and it is the mother who often has to give up her career and income to care for their PKU child.

It is also unethical to restrict a person with PKU’s career choice by not offering them access to a pharmaceutical treatment which would allow them to freely chose their career, eg enter the armed forces. Instead, they face restrictions in their career choice because the only option available to them is dietary therapy which is not compatible with all career choices.

Q10. NICE should make KUVAN available to PKU patients of all ages, genders, disabilities and during maternity and pregnancy if it is safe.

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. It is not stated whether the transition would take place in child or adult care services and no costings for additional services have been factored into NICE's cost analysis.

There are currently issues with transition from child care services to adult care services and these need to be resolved before adding change of therapy into the mix.

NICE need to take into consideration the promises and commitments made by the UK Government, Department of Health, to people with rare diseases like PKU, such as

"...we aim to ensure no one gets left behind just because they have a rare disease"

"We want to put the patients' needs first."

"The UK will take action... by empowering those affected by rare diseases"

"The care pathway will include.....the development of seamless pathways for transition, from childhood to adolescence, and on to adulthood and older age"

The Draft Guidance on Kuvan does not meet these aims and commitments.

I urge you to amend the Draft Guidance to ensure that PKU patients of all ages are offered fair and equal access to Kuvan, regardless of their age, sex or disability and that the dosing guidance is per the manufacturer instructions so that the dose range will be sufficient for adults too.

Respondent 108

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. PKU is a genetic condition which requires life long management, it doesn't just dissapear when you turn 18!

Q3. NICE's statements are contradictory

Q4. There are still side effects which indicate neurological deterioration after you turn 18 caused by high PHE levels.

Q5. My levels are often high, I have had mental health issues since even before turning 18 which continued and got worse in adulthood and I'm sure the high PHE levels have contributed to this.

Q6. It is extremely important to think of future issues PHE levels cause and cost should not even be a factor, you can't put a price on someone's health.

Q7. I think levels definitely affect mental health as I have suffered myself, been on medication and received therapy, so I'm sure there are significant costs that can be associated with PKU.

Q8. Kuvan could definitely improve family life and lesser the stress PKU brings on every day activities and lifestyle.

Q9. That is very unfair, as an adult I can confirm it is a massive phycological battle to make sure you consume the right foods and mental health can add to the stress and difficulties. Unless a person lives with pku it's extremely unfair for them to make judgements as they do not understand the difficulties we face.

Q10. When it's so vital a pregnant woman keeps her PHE levels down to make sure the baby devolps healthily, I think its highly unfair to say pregnant women wouldn't benefit as they are the group who would most benefit from kuvan.

Q11. When your pregnant, you can stick to your diet religiously, but if you're ill it causes your PHE levels to rise uncontrollably which is one factor demonstrating the importance of kuvan.

Q12. You can't put a cost on health

Q13. PKU is a life long condition, it's very hard to live with and causes many challenges. The fact that cost is being considered over peoples quality of life when there is a drug available that can help is absolutely diabolical.

Respondent 109

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. *[no response given to this question]*

Q3. I do not agree with NICE's view

Q4. I have seen behavioural problems due to protein being taken too much

Q5. In my experience this is added to be feelings of self harm

Q6. I feel every day living with pku has an effect, child or adult. Mental health is a very important area to look into.

Q7. Yes absolutely there will be coats involved. Mental health for those with PKU is every bit as important as that for those with any condition. Self harm has been a problem

Q8. The family members cope well. This may be due to their profession/experience of this.

Q9. I feel treatment is good throughout but people may not feel they can reach out.

Q10. I M aware of the need for specialist care during the run up to pregnancy/. This has been made very clear

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 110

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Yeah quite frankly it's vile. First to tackle tackle taking it away at 18???? They would NOT be able to adjust and it would be such a shock to the system the low protien diet just wouldn't be sustainable. I don't care what the advice that has been given is at 18 this would still have detrimental effects to the person in question. As someone with PKU who is 20 nearly 21 I know first hand the struggles, and an imbalanced diet due to this medication being stripped and an almost impossible task of having that low level of PHE could cause anxiety, depression, Motor problems that would all effect the life. I was so depressed off diet I tried to kill myself. Purely because of medical imbalance??? Anyone who knows me would/ has been SHOCKED by this fact. Quite frankly to take it away at 18 does more harm than never giving it to them. Then to ignore that look at all the countries that offer it??? It should be avaible
To everyone it is life changing? I have been susceptible to anorexia purely because all food except fruit veg and oils to cook with have been taught as guilty and I will not type anymore because it's waste. No one will ever understand unless they have it? I respect the people who try and do it even for a week SO much but a week compared to your whole life? To always have those repercussion? It's incomparable? Also the damage to unborn children during pregnancy cannot be commented? All women should be able to get this. When I was 17 and off diet I fell pregnant by mistake I was on the pill and responsible but by the time I realised i felt the only option was to have an abortion Due to the damage to my unborn child. The guilt that came with this was extreme and anyone who has the power to prevent this happening again absolutely should. I don't know what else to say because there is so much but seriously re evaluate what you even know if anyone is genuinely debating this???

Q3. I do not agree with NICE's view;NICE's statements are contradictory;This is complete bullshit??? PHE is toxic to the brain??! Just look at the studies on white/grey matter, cognitive function etc like I don't really know who came up with this????

Q4. I have a tremor, I have shakes, I can't think the same and when I had slightly too much PHE I had debilitating anxiety because of the way receptors and processing is altered. This may be a small number of people but the effect is vast and worth preventing.

Q5. This is completely correct and still massively underestimated the impacts. Re asses the science

Q6. *[no response given to this question]*

Q7. I was treated by CAMHs and other gps for side effects, I believe this could have been avoided without PKU or KUVAN

Q8. *[no response given to this question]*

Q9. *[no response given to this question]*

Q10. CHECK THE SCIENCE the damage to unborn children is fact. I had an abortion at 17 when I was off diet because I felt the damage was so sever they wouldn't have a normal life.

Q11. Pregnant women get cravings? Pregnant women's metabolism changes, hence potentially losing muscle (which would case an increase in PHE LEVELS) would need to eat properly?? It's crucial and could change many people's lives immediatily

Q12. I think this was calculated?? Why would they wanna look a the cost? Why would they wanna imagine spending money in the short term could save long term. This just needs major reevaluation

Q13. I think no one can truly understand how it feels, I'm crying writing this and I don't expect anyone except someone with PKU to understand because how could you?? Please please please reconsider the difference it would make to so many lives is so vast and it's already used in so many countries which makes it harder. If I could afford it , even if it was ALL MY DISPOSABLE income I would still pay for it. It's the mental and physical health. It isn't even about the food because now with all the vegan options etc it's so easy for food. It's about the quality and life and health (physical and mental) and I think you can't put a price on that

Respondent 111

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Negotiating puberty for a young person is very challenging and is massively more so for those with PKU. Many teens come off diet and they are excluded from many aspects of life that they see their peers enjoying. I was one of these such teenagers. The self control required to go against the flow when peers are free to eat and drink whatever they like was a huge hurdle. As such, I, as many other young people, developed an eating disorder. There was no psychological help and no treatment for PKU other than diet. This was at the time of my GCSEs and A Levels. I did not achieve the A Levels I had hoped to therefore my life choices were more restricted than they might have been without being off diet. I

then went off to my 18 yr old independent life, off diet. By 21, my mum and only dietary carer, had suddenly died and I was left with no metabolic team and no help and no diet. I got symptoms. I was anxious and I had pins and needles. My MRI showed demyelination. I found a metabolic team and went back on diet. You can imagine what a difficult time this was at my age and how difficult it had been struggling to be away from home and learning to live alone and learning my diet of self restriction after 7 years off diet. Stopping offering Kuvan to 18 year olds would be the cruellest ‘treatment’ of young people at a vulnerable time of their lives. No diet for 18 years then full restrictive diet and unpalatable supplements without Kuvan would be disastrous and unmanageable; impossible, even.

Q3. NICE's statements are contradictory

Q4. I can tell you that, I’m my 7 years off diet, I had actual neurological symptoms. I had numbness to a pin prick in my leg for months and numbness in my tongue and side of face. I also had anxiety likely from being off diet and too high Phe. Coping away from home as a young adult was much harder, being PKU. My MRI showed demyelination and I was told I may develop MS. This was ignorance on the part of my GP. I was not going to get MS but he told me I would on Christmas Eve. My metabolic team told me that going back to full restricted diet and supplements would put things right and it did. I do not have MS. If I only could have had Kuvan at that age and up until now, I could have avoided any of that episode and avoided having to return to a highly restricted diet.

Q5. I have a well maintained diet now purely by my commitment to my health and by will power and the prescription foods and supplements. I can recall all these descriptions as being true from when I was off diet for 7 years at the time of my GCSEs and ALevels and three years of university life.

Q6. Considering NICE has advised the NHS that a treatment for preventing type 2 diabetes in those with a BMI over 27 is essential for cost of patients to the NHS and for their quality of life, I am assuming they would of course be entirely equitable in their consideration for those adults with PKU. Yes, past high Phe levels can affect the future of PKU patients - there are papers written that I have read evidencing the lower life changes of those with poorly controlled Phe levels. One such paper suggested those who had had uncontrolled diet were more likely to be single and to be in lower paid work and even involved in crime. There was a direct correlation between high Phe levels and poorer life chances in the future.

Q7. I maintain a well controlled diet because I make myself because I don’t want symptoms and so I have not cost the NHS other ongoing costs that I believe are related to PKU. A GP did once get his calculator in my appointment to find out how much I cost his surgery, which was pretty shocking to a twenty something year old and highly unprofessional. I believe costs for associated problems could be very high to the NHS.

Q8. The impact on family members should definitely be taken into account. It takes over 19 hours a week and for families, getting DLA or PIP is incredibly hard, if not impossible. The impact of someone having to adjust their careers to care for a pku patient should be very much taken into account.

Q9. To withhold Kuvan from the vulnerable groups listed would be discrimination against those people and appalling, especially if the reason cited is “due to costs”.

Q10. NICE should of course recommend the NHS provides this additional support to women who face the even more highly restricted pre conception diet and pregnancy. I have had 3 children for whom I have followed the PKU diet with metabolic dietitian help. To have had Kuvan through these pregnancies and befor would have meant I would not have been hungry and would have found it much easier to do my job. Taking 150 Phlexy 10 capsules per day takes some time when you are a teacher with a lunch time club to run. You usually have to choose whether to eat or take the capsules in the few minutes available to teachers. It is practical things such as these that would make Kuvan one of the best things for adults with PKU.

Q11. Being threatened with abortion if I were ever to get pregnant, when I was younger, made the whole area so much scarier as a young woman growing up. When you are pregnant there is a constant worry that you are doing the right thing and eating the right things for your baby - this goes way deeper than for non PKU women. Control on pregnancy is vital and, as Kuvan exists, it should be available to PKU women to protect to rid babies and to protect the NHS for when their babies are born.

Q12. I have explained the neurological symptoms I had off diet and I know these would have developed had I not taken control again. The neurological costs must be calculated.

Q13. NICE has so far done half a job in their considerations. If nothing else, they should look at how equitable their offer of Kuvan is to PKU sufferers, by neglecting to offer it to over 18s, compared to treatments funded for use by adults with type 2 diabetes and other lifelong conditions affected by diet.

Respondent 112

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. This Decision to stop treatment of PKU for the 18 and above is lunacy. This would be like giving a struggling child an Inhaler and then telling them they no longer need it just because their 18th year has past. The long term effects of PKU are astoundingly difficult and allowing a child to eat almost anything as they grow and then telling them the rest of their life must be limited and controlled in regards to eating when they have had their entire childhood to develop tastes and habits is wholly wrong and a step in a direction where we could see huge cost and huge detrimental mental health issues for years afterwards, this isnt economic by any means and it's almost inhumane to give a child a drug and then allow them to go cold turkey just because they are an adult.

Q3. I do not agree with NICE's view;Long term brain damage is a whole wider Gamut of discussion. Factually and simply a PKU adults brain and thinking and higher function can be effected in as little as a few hours. It ruins relationships it ruins careers and it ruins Lives.

Q4. There is a study to suggest that even the carriers of PKU are prone to mental health issues and long term emotional difficulties as well as full PKU patients. Brain damage is a huge subject and I as a PKU patient experience side effects of high PHE levels in a matter of hours. This hugely can damage a person's cognitive and physical abilities even more extensively over time.

Q5. High Phe Levels effects not only the people with PKU but even the people around you..... to a point that they can find you very hard to live with.

The people who live with A Pku adult only understand what the conditions of your condition through a lense. They do not understand the confusion the anxiety the lack of coping mechanisms. Sometimes those people forget that you are not always aware of your self and your mood and your aura and sometimes they just wish you were somewhere or someone else. It has been described to me as living with Jackal and Hyde. Sadly.....

Q6. Yes because a PKU patient with high phe levels can loose the ability to cope and strategise effectively their own lives. It costs a great deal emotionally for a person to cope with their mental chaos and lack of empathy for others. Sometimes it makes you not very popular.

A person with Asburgers syndrome can be treated for their symptoms and trates to a point but a PKU patient with high PHe levels can inhibit some similar behaviours yet receives no real support aside from supplement.

Q7. There are significant issues for PKU Patients with GUT health issues. Alot of acidic formula designed for the treatment of PKU are made from abattoir waste. Do we really want our loved ones living the rest of their lives dependant on that stuff ?

Q8. *[no response given to this question]*

Q9. *[no response given to this question]*

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. This is the fundamental reason why this should as a priority be offered first and foremost to women of PKU who are trying or having a Baby. This is detrimental.

Q13. *[no response given to this question]*

Respondent 113

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I think the concept of stopping kuvan at 18 years old is grossly unfair. By this point it's unlikely a person will have developed sufficient knowledge and skills for effective low protein diet. My own experiences relied on my mother religiously taking time to provide appropriate meals and sharing knowledge to myself for education. Ultimately taking kuvan away from someone at the age of 18 without sufficient knowledge base is going to lead to poor pku dietary concordance therefore detrimental long term effects as a adult.

Q3. NICE's statements are contradictory

Q4. As an adult with pku I have encountered many problems such as anxiety; depression, brain fog and difficult in processing information. The advice has changed since I became a adult as suggested 'relaxed' diet (eg. No meat or fish) but the evidence now suggests life long strict pku diet required. Therefore like any research; I'm sure recommendations for best practice will change again as we know more from relevant research trials.

Q5. My own personal experiences have confirmed the above symptoms when my pku diet is not as tightly controlled. It's very hard to maintain compliance every day and experience good quality of life.

Q6. Yes. Mental health life with any situation or experience will have life long effects. My own experience to name one; was when my dietician was unfamiliar with my protein substitute shakes and prescribed double the amount. This led to weight gain and low self esteem which has been difficult to recover.

Q7. Health care costs associated with pku must be high. As measurable cost is the protein substitute medications taken (I currently take 85 tablets a day) which my pharmacist states costs around £1000 per month if correct. Also low protein substitute foods are expensive. Then secondary not as easily measured costs will be associated with anxiety, depression, vitamin supplements etc and impaired quality of life eg. Difficult to eat out or go away etc. Life everyday involves dietary management and it's unrelenting.

Q8. Yes. As effects quality of life in terms meals out, holidays, family events as diet management needs to be planned. Time at the weekends is needed to plan meals or even prepare meals ahead for busy days managing a young family.

Q9. We are equal and all have our own problems and challenges with low protein diet concordance. Equality has to be fair for all pku sufferers.

Q10. Grossly unfair. I've had two children. I had to visit hospital for blood tests twice a week, plan meals as working and tired with pregnancy itself. I had to take more protein substitute tablets too (145 tablets a day!). Anxiety of what I was eating and the potential damage/ harm to my unborn child and created disorder/ problem with eating food. It's tiring and unrelenting periods of my time.

Q11. I had to take more protein substitute tablets too (145 tablets a day!). Anxiety of what I was eating and the potential damage/ harm to my unborn child and created disorder/ problem with eating food. It's tiring and unrelenting periods of my time

Q12. I do not agree. As when measuring healthcare burden the associated costs from managing and utilising healthcare resources to manage neurological conditions will lead to significantly increased healthcare expenditure overall.

Q13. I think the overarching message I would like to be considered is holistic healthcare approach to low diet pku management.
There are healthcare costs easily measured but many additional healthcare factors such as anxiety that need to be considered for prudent pku healthcare management.
Kuvan has been available in other counties for several years and eagerly awaited in the UK. It has proven efficacy and cost effective for pku patients.

But we need to please remember the impacts on quality of life and in particularly the detrimental impact it has for all adult and child pku sufferers and their families.

Respondent 114

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Absolutely shocking that support would be given to manage the condition until a point in life when patients would be starting university/apprenticeships/work moving home and becoming independent. How can these people be expected to cope with their condition by suddenly treating it in a way they never have before, completely having to change their lives in order to keep up their current levels of neurological health? I struggled to continue on diet when I first went to university, I would certainly not have coped with a new life limiting treatment plan.

Q3. NICE's statements are contradictory

Q4. The evidence of negative impact from prolonged high levels of Phe in the system is overwhelming. All patients are advised to follow diet for life for that reason and this has been the case for a generation.

Q5. I absolutely agree that once you have high phe levels, getting yourself back in track is incredibly hard. I have experienced this to a greater degree during this pandemic too, unable to prioritise self care when struggling with mental health lows.

Q6. I have already pointed out that 18 year olds are often at pivotal moments in their lives. To suddenly experience long term high levels of phe at this point would absolutely affect their lives and futures.

Q7. As with all chronic conditions health care costs are very hard to quantify when symptoms and conditions linked with the overall condition are taken into account as each experience and reaction is so different. But, there absolutely will be a substantial cost involved in treating the physical and mental health of an adult with long term high phe levels.

Q8. PKU affects a whole family, not least as it affects sharing meals, celebrations, holidays. I especially would expect consideration for women with PKU and their partners when trying to start a family. I have experienced managing maternal PKU. It is incredibly hard work and affects many people.

Q9. To list so many groups that would be affected and conclude still that no help is needed for adults seems ridiculous to me. And surely bringing a baby into the world with avoidable disability is creating greater health care costs?

Q10. Surely, even though evidence of benefits to an unborn child may be limited, there is abundant evidence of damage to an unborn child who hasn't received close antenatal monitoring of diet? I would ask NICE to call some PKU mothers!

Q11. It breaks my heart to know that women have had babies without support and regular treatment and those children have had to live with disability as a result. Phe level control for my first pregnancy was hard, with a new baby in the house was harder and the second time around was physically and mentally draining to the point that now I have a small young family I feel managing the diet so closely a third time in our current daily routine would be too difficult. Considering my condition has been a big factor in the decision to not have any more children.

Q12. Neurological damage to unborn babies, which could have been prevented, must incur a high, long term health care cost. It's obvious.

Q13. I understand that costs are a worry, especially when treating life long conditions. But this report is full of contradictions, not least that brain development continues until 25 and it's decision to stop treatment at 18. I feel there is also a gross understatement (or no statement at all) regarding current ongoing health costs of high phe levels in adults and neurological conditions in infants of untreated mothers.

Respondent 115

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Being an adult with pku I think this is unfair. Adults with pku suffer from all types of symptoms if we have high levels. Kuvan should be allowed through adulthood as well. I suffer from headaches, concentration issues, seizures and social anxiety among other symptoms because of high levels. I try to keep my levels as low as possible but Kuan would be a life changer and the cost of diet is so expensive to the NHS.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. A pku brain has much water and proteins on it due to high levels of phenylalanine. This has to cause problems in adulthood and I have experienced problems as have many adults I know who are struggling with their levels.

Q5. Quality of life is reduced with high phe levels and depression is a big side effect of this. I am on medications for depression and anxiety due to the effects of high levels.

Q6. Yes

Q7. I have IBS and struggle daily and and have I have said previous I suffer with many side effects.

Q8. *[no response given to this question]*

Q9. *[no response given to this question]*

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 116

Q1. *[no response given to this question]*

Q2. I remember when I was growing up and particularly as a teenager how difficult it is not being able to join in with my friends and peers whenever food was involved. This was any snacks , formal meals, takeaways, school trips and holidays. It also included some drinks as well, due to many not being allowed. I have a low exchange allowance so this impacted on me a lot.
As an adult this has not changed. I avoid going out with meals with work, which is a very difficult situation, coffee shops are difficult with limited options and even a drink in the pub if I want soft drinks! I never go to hotels and always have to go self catering.
I have suffered and still do, with anxiety, do not feel able to ask venues to make changes to the menu (most places do not even have one item that is fully free of exchanges!) I feel restricted and very low about this situation on a regular basis.

Q3. I do not agree with NICE's view;THis does not take into account the feelings of brain fog, headaches, tiredness, lack of concentration, depression and anxiety due to higher levels

Q4. see above

Q5. This effects all aspects of life, personal and professional.

Q6. See above commentsCost

Q7. Depression, anxiety treatment. Cost of all low protein food etc

Q8. Living with a person with PKU when their PHE levels are high have an impact on personal relationships

Q9. *[no response given to this question]*

Q10. *[no response given to this question]*

Q11.
The diet before conception and during pregnancy is so much stricter and far more difficult to manage than normal. Having a pregnancy with PKU is huge challenge to control PHE levels and the stress of knowing high levels can damage the baby is very stressful and has an impact of the emotional wellbeing whilst pregnant. Having constant sickness and not being able to always tolerate your supplement will raise your PHE levels, any infections will do the same.
It is unbelievable that Kuvan is not considered vital to prevent harm to the unborn child!

Q12. My daughter who does not have PKU has been followed up since 4 weeks old with regular appointments and regular IQ tests during her life to the age of 16. There is obviously a cost implication to this!

Q13. *[no response given to this question]*

Respondent 117

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Here's the thing! My older brother has PKU so I have lived with it all my life.

From the age of about 16, my mum no longer had the full control she had over my brother's diet that she had when he was younger. He began to reject the constrictions of a PKU diet and at the same time, he got all the brain damage symptoms of high PHE levels which made his life, my parents life and my life HELL. (see Section 3)

At 18, he was refusing to go to school and scraped through his A levels, even though he is really clever! His university accepted him, not based on his A level results (which were a bit crap), but because the uni was so impressed by him, on a personal level and what he achieved despite his health condition, they let him in.

But.....when he left home to go to university at 18 years and 3 months old, it was like being fed to the lions! .....how on earth could he manage everything a fresher has to cope with on top of managing this own very complicated health issues all by himself for the first time?..... There are so many aspects to having PKU and having to eat a "special diet" is literally just one aspect! .....It all went drastically wrong. Heartbreaking for him and the whole family - very, very traumatic times. Even getting prescriptions from the GP surgeries was a drama - and he was met with bossy receptionists who made him feel bad for ordering pasta or rice. Some even asked why he didn't buy it in the supermarkets like everyone else, as gluten-free products are now available in the shops!! It used to upset him, the ignorance and the discrimatory remarks.

Stopping medication at 18 and switching to harder, longer diet therapy? What do I think? 18 is such a crucial stage in our lives - ..... How on EARTH could you give a child a drug for up to 18 years then thrust them onto a crappy diet on their 18th birthday PLUS expect them to MANAGE all that goes with it by themselves? It is senseless! You need to live with a PKU family and get a real life, lived experience of what it is like living with PKU ---- because, I can assure you, if you knew, you would not even think of doing this to an 18 year old! It's INSANE.

Young people's mental health is such a BIG ISSUE at the moment, especially with the effects of the pandemic ..... how can you justify morally, ethically or legally basis KNOWINGLY putting at risk the mental health of a specific set of young people who are actually medically known to be susceptible to mental health issue by way of their medical condition?

You have no right to play with people's lives like this.

Q3. I do not agree with NICE's view

Q4. -which it ca do The fact that you have written "There is no risk of long-term brain damage in adults" astounds me. It shows that, with the thousands of pages of text you have had to consider whilst carrying out this appraisal, you have ignored one thing, so I shall remind you of Donald Rumsfeld's well-known quote:

"There are no "knowns." There are things we know that we know.
There are known "unknowns". That is to say there are things that we now know we don't know.
But there are also "unknown unknowns". There are things we do not know we don't know.

Mr Rumsfeld also said "There's another way to phrase that and that is that the absence of evidence is not evidence of absence".

The human race cannot, at this stage of our development, categorically say that there are no long term effects of brain damage on PKU adults. We don't yet know the significance of the white matter changes in the brain and whether there is a link with dementia. We don't yet know the effects on the gut biome of the PKU diet or of changing therapies from medication to diet. We don't yet know the effects on the oral health of PKU patients - a very real problem that is only coming to light now we have social media and can exchange experiences. We don't yet know the effect of PKU on the bone structure and whether there is a connection with early onset osteoarthritis.....

However, in our lived experiences, we know that there is long term brain damage in PKU adults that hugely impacts on their life and this is why my PKU brother is classed as having a disability.

The definition of disability under the Equality Act 2010 (EA 2010) is that you're disabled if you have a physical or mental impairment that has a 'substantial' and 'long-term' negative effect on your ability to do normal daily activities.

'Substantial' is defined as more than minor or trivial. The mental impairment from PKU-associated brain damage and the knock on effects it has on every aspect of their life of a person with PKU (hopes and dreams for the future, education, ability to hold down a job, career choices, to build social relationships) is HUGELY substantial.

'Long-term' is defined as meaning 12 months or more. The mental impairments caused by PKU alone, last for much longer than 12 months and can shape a person's life and personality in so many ways.

Unless NICE have a different definition of "long term " to the definition of a "long-term" in the way it relates to a physical or mental impairment under the EA 2010, as recognised by the DWP and the UK court system for the purposes of awarding Personal Independence Payments, then the long-term effects of PKU-related brain damage can be and are considered a disability.

LONG TERM DISABLING EFFECTS OF PKU on my brother that he can't get back or reverse now include:

- Low self-esteem, self confidence and distorted body image (affects relationships)
- Lost years of childhood, meeting girls and going out with mates
- Underachievement in education
- Underachievement in job prospects
- Long-lasting and possibly life-long mental health issues (depression, eating disorders, anxiety)
- Bad teeth (from years of self neglect whilst in depressive episode) + related dentristy expenses
- Painful headaches, causing aggression and irritability

He got depression, anxiety, social withdrawal, he makes irrational decisions, he can't focus or concentrate, he gets aggressive and completely "loses it", he shakes, he gets seriously bad headaches, - if that lasts for more than 12 months , then that's 12 months of living a life with brain damage that he might not have to go through if he were able to take KUVAN.

Q5. It is really difficult to get you to see.....
This is a VICIOUS CIRCLE.

High PHE levels cause brain damage effects ['brain fog', forgetfulness, fatigue, low mood and feelings of irritability, irrationality, headaches, depressive episodes, anxiety etc etc.]

Brain damage effects hinder you from adhering the PKU diet. You might make irrational, bad food choices, you might forget to take your supplement, you might stop eating all together, you might be too tired too eat. You might get into bad habits,

Hinderances from adhering the PKU diet lead to high PHE levels.....

Once you are in this cycle, it takes a willpower of steel to get out of it. Lots of PKU people can't. My brother is in a constant struggle with his diet. I don't know if he is capable of getting back onto it. It's sad and hard to see.

Q6. Of course it is neccessary to take into account the long term effects of phe levels in adults when calculating cost effectiveness.

The decrease in the requirement for mental health cares cost alone (if the service was adequate and easily available/accessible in the UK) would justify itself in cost effectiveness alone.

Everything about having phe levels has effected my brother's life and that of all our families. It is central to everything we do, we eat, to family gatherings, to the concerns for his education, for his university studies, for his career prospects, for him being able to lead an independent life, for his wellbeing, for his mental health and for OUR HEALTH and wellbeing too!

Q7. Dental costs
Gut Problems
Therapy for mental health issues

Q8. My mum gave up her well-paid job to look after my brother when he was younger.

She then re-trained as a lawyer when he was in his teens, only for all that re-training to go to waste when she had to give up work again because the teenage years/young adulthood turned out to be the hardest in terms of caring for someone with PKU.

She now has very little earning power and it is difficult to get back onto the career ladder when you are past 50.

Q9. NO.

The draft Guidance discriminates on patients over the age of 18 on the basis of age, their disability, and against pregnancy and maternity. It is also indirectly discriminating against women (sex discrimination) by way of ignoring carer disutility

Q10. NICE should approve KUVAN for use in all ages but particularly for women of child-bearing age. If Kuvan alleviates the horrid experience of fear of PKU maternal syndrome pre-conception and throughout pregnancy, then it is cruel to deprive women of it.

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. Has NICE considered the human rights and human development aspects of this decision?

The United Nations Development Programme defines "human development" as "the process of enlarging people's choices," choices which allow them to "lead a long and healthy life, to be educated, to enjoy a decent standard of living," as well as "political freedom, other guaranteed human rights and various ingredients of self-respect." - United Nations Development Programme (1997). Human Development Report 1997. Human Development Report. p. 15

The decision to offer a new medical treatment to a certain subset of humans with PKU (0-17) whilst refusing it to all other humans with PKU (18+) is:

- not enlarging their choice to lead a long and healthy life (by only offering dietary therapy, particularly to those for whom it is unsuccessful or impossible, you are actually taking away their choice to lead a healthy life),

- adversely impacting on their ability to become educated (by causing stress and anxiety to secondary school pupils knowing their medication will stop soon and to 18 years olds who would face going to university/starting their work life with the additional burden of adapting to and managing an extremely onerous and time-consuming dietary therapy),

- adversely impacting their abiliity to enjoy a decent standard of living (if they have under-achieved in their education and/or suffer poor mental health and other illnesses because they are under-or untreated, they may find it difficult to hold down a job or work full-time which would impact on their finances)

_ taking away their human rights and self respect by deeming them not important or valuable enough as a human being to deserve new and innovative treatments for their condition, leaving them with no options or choices.

The MHRA Innovative Licensing and Access Pathway was issued in January this year.

In it, Lord Blethell says "We are absolutely determined to make sure UK patients can access the latest cutting-edge medicines as quickly as possible to help everybody live longer, healthier and happier lives. .....THIS MUST APPLY TO PKU PATIENTS TOO!

Dr June Raine CBE, Chief Executive, Medicines and Healthcare products Regulatory Agency comments: "Transforming the way innovative medicines reach patients in the UK is not a ‘nice to have’. It’s a ‘must do’. An imperative. And the time to do it is now". PKU PATIENTS OF ALL AGES DESERVE TO HAVE THE OPTION OF TREATING THEIR CONDITION BY KUVAN, AND NOT BE LEFT UNDER- OR UNTREATED BY DIETARY TREATMENT OPTION ALONE!

IT IS WRONG of NICE to approve the use of a medecine in a way that discriminates against age, sex, disability and pregnancy/maternity.

It is also wrong for the Department of Health and Social Care, NICE and NHS to blatantly risk the health of people with PKU over the age of 18, who are known , by refusing to allow them fair and equal access to a medication which might alleviate the mental health issues caused by that condition

It is also evil for the Department of Health and Social Care, NICE and NHS to openly acknowledge that PKU patients of all ages are susceptible to mental health issues because of the way their condition affect the brain, but then blatantly refuse to offer them fair and equal access to a medication which might alleviate those mental health issues unless they fall within a certain age group. This Draft Guidance must be changed to provide FAIR and EQUAL healthcare options to all people with PKU, regardless of age.

NSPKU questionnaire responses – children
ID1475 sapropterin for treating phenylketonuria

Questions

Q1. **Section 1 Recommendations: Do you agree with NICE's recommendation which says that: Sapropterin (ie Kuvan) is recommended as an option for treating people with PKU only if they are under 18?**

Q2. **Section 1 Recommendations : Do you have comments on the proposal to let children take Kuvan (sapropterin) until the age of 18 and then stop? (Experiences which might be relevant are - getting children accustomed to their diet, or about being a teenager with PKU and learning to manage dietary treatment on your own.)**

Q3. **Section 3 - Long term brain damage in adults - NICE has said: "...adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25." NICE has also said "and there is no risk of long-term brain damage in adults". What is your opinion on NICE's statements about brain damage in adults?**

Q4. **Section 3 - Long term brain damage - Do you have knowledge or experience about long term brain damage in adults? Is there any evidence you want NICE to take into consideration (including from your own personal or family experience?)**

Q5. **Section 3 - Effect of PKU on carers : NICE said PKU can have an effect on carers/families of children with PKU. They said "... carers of children with PKU also report additional difficulties related to diet management. These include strains on their relationships, struggling to get the right support, and having to give up work or working part-time to dedicate more time to diet management. They also need to educate professionals, teachers, other children's parents, their families, and other carers about PKU and the diet restrictions. The known risk of irreversible brain damage if Phe levels are not controlled is a permanent source of stress for carers. The committee concluded that people with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet." Do you agree? Do you have additional comments?**

Q6. **(Carer disutility) - NICE made an "economic model" to value how much Kuvan was worth. NICE did not take into account the effect that PKU has on family members that help look after children or teenagers with PKU in their economic model. Do you think NICE should have taken into account the impact of PKU on other family members when valuing treatments for PKU? Do you have experience to share?**

Q7. **NICE said that "Children with PKU frequently experience difficulty with focus, depression or anxiety, disordered eating, digestive problems, headaches, low mood and sadness, feeling tired all the time and being in a heightened emotional state (including aggressiveness, psychosis and paranoia) because of high Phe levels. The committee concluded that there is a need for a treatment that can reduce PKU symptoms and give people with PKU and their carers peace of mind about blood Phe levels. " Do you agree or have additional comments? Do you have experiences about other health problems associated with PKU?**

Q8. **Costs associated with supporting families who are struggling with PKU and its effect on quality of life. NICE identified that there may be costs associated with supporting children/families who are struggling with PKU including extra support from the metabolic team, extra support in school and social services. NICE said that information is not routinely collected on long-term brain damage because of PKU or the number of children referred to early help services and social services, and the costs involved. They said but there is little evidence available to estimate its effect on the quality of life of people with PKU. Do you have any comments or life experience to share?**

Q9. **Equalities - treatment of different groups. NICE said some people may have greater difficulty managing PKU through diet. NICE have said the groups of people who may be disadvantaged include - "People who face such difficulties include: people with a learning disability, sensory impairment, or cognitive impairment• autistic people and people with comorbidities such as diabetes and gut disorders• people on low incomes, living in poor or in insecure housing• certain ethnic groups including people who do not speak English and Gypsy, Roma and Traveller communities• people in social care settings• women with PKU who need to establish controlled phenylalanine levels before conception to avoid damage to the unborn baby." NICE concludes that it was not possible to recommend KUVAN in any group of adults "due to the cost effectiveness estimates in adults". Do you have comments about some people who have extra problems managing PKU because of their situation? Do you think NICE has properly considered treating people fairly?**

Q10. **Women with PKU and their children - NICE has said : "The committee was not aware of any evidence to estimate the benefit to the unborn child of enhanced Phe level control or greater natural protein consumption from conception to birth and accepted that this is challenging to model." NICE has not recommended Kuvan (sapropterin) to help women manage the risk of Maternal PKU. What recommendation do you think NICE should make?**

Q11. **Women with PKU and their children - NICE has said they welcome comments and further evidence on the potential use of Kuvan (sapropterin) in women with PKU of childbearing age, or those planning pregnancy, to prevent harm to the unborn child. Do you have comments or evidence to give to NICE?**

Q12. **Women with PKU and their children : NICE has not included the costs of preventing neurological damage to the children of women with uncontrolled PKU (ERG report, section 5.5) in their costs calculations. Do you have any comment?**

Q13. **Do you have any additional comments on the draft recommendation or the evidence NICE has considered?**

Respondent 1

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. My partner struggled with her transition to adult care without kuvan, and this would be even harder for kids who have to transition from a life-changing drug to their own management

Q3. I do not agree with NICE's view

Q4. My partner with pku had a brain scan and it was reported that she had excess white matter, squashed pituitary gland and intracranial hypertension.

Q5. I agree with this. As a partner of a PkU person you must be on hand to help and care for them especially when their phe levels are high and they struggle with daily tasks and care

Q6. N/a

Q7. Yes, my partner with pku has bipolar disorder and borderline personality disorder in addition to many of the problems listed above

Q8. N/a

Q9. N/a

Q10. N/a

Q11. N/a

Q12. N/a

Q13. N/a

Respondent 2

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I don’t think it is fair stopping the treatment at the age of 18. If you’re receiving the treatment all through your child hood and the it suddenly stops, it won’t be easy to adjust to another diet when you’ve been used to eating a lot more protein throughout your childhood whilst taking Kuvan.

Q3. I do not agree with NICE's view

Q4. I do not have any personal experience of it but I would not want to take the risk of going on to a normal diet and then potentially damaging my brain due to eating high amounts of protein. The Kuvan pill would make me feel a lot more comfortable eating as close to a normal diet as possible.

Q5. I do agree with this. Both myself and my sister have PKU and it put a lot of stress on our parents who had to make sure we were catered for in such way that wouldn’t harm us. They were constantly stressed about what to feed us over the years and the Kuvan pill would certainly have helped relieve that stress.

Q6. Absolutely, the should be taking into account the impact it has on parents and siblings. My sister and I both have PKU but we also have 2 other siblings who don’t. However, they were impacted many times as a lot of the time the family would be eating the same low protein meals as me in order to make life easier. This meant that a lot of the time, my siblings and parents weren’t getting the nutrients they should be as they weren’t eating enough protein whilst having similar meals to a PKU

Q7. I completely agree with this and I also experience all the above symptoms as a young adult (22 years old). The Kuvan pill would certainly help in keeping my PHE levels down and hopefully allow me to live my life more comfortably.

Q8. PKU certainly affected my life growing up- especially in a school environment as I was looked at as a freak because I couldn’t eat the same as everyone else. I know for a fact that the Kuvan treatment would’ve made school and easier experience for me. Even now as a young adult playing professional football hasn’t been easy for me on a PKU diet as I feel I am not getting enough protein in to help recovery abs muscle growth. The Kuvan pill would allow me to have more protein which would hopefully improve my performance levels.

Q9. I don’t have any personal experience of the above but I don’t believe NICE have properly considered treating people fairly.

Q10. I think NICE should consider allowing pregnant women the Kuvan treatment as it would certainly take a bit more pressure off them with how strict the PKU diet is during pregnancy.

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. I think people of all ages should be allowed Kuvan treatment. I have lived 22 years on an incredibly strict diet and faced so many different challenges because of PKU. Kuvan would allow me to live a more normal life without the stress and anxiety of potentially damaging my brain.

Respondent 3

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I dont think it is fair to take kuvan away from them when they are 18.PKU doesnt stop when they turn 18 it is a lifelong condition.i think this would have a huge impact on their mental health leading up to when they turn 18 knowing they would have kuvan taken off them soon as well as after turning 18.being allowed abit of freedom with their diet to then go back on not the nicest of diets would affect them massively

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. I do agree.from the moment my daughter was born it was stressful and emotional.having to work everything out and having to say no to certain foods her friends and family have isnt a nice feeling i wanted to feel.it only gets worse when they hit the teenage years,when going out with friends or sleeping out makes it harder and they get upset about not being normal.when my daughter starting college it was stressful too,explaining to her teachers about everything and new friends about her diet was hard for her.alot of arguments and tears we have had over the years takes a toll on myself and my daughter

Q6. Yes i think they should of looked at the impact it has on everyone.its hard for children with PKU but also parents,siblings,grandparents etc.having to adapt to it when born was hard enough but living with it through the years as they grow up is tougher. Especially when they younger and dont understand why we say no to things but their siblings and friends can.

Q7. Having PKU affects my daughter alot.she sufferers with problems trying to focus,her head always feeling foggy,anxiety,headaches and migraines,acid reflux,shakes in her arms when not eaten enough and always tired.dealing with these everyday is a struggle,she takes loads of medication for a few of these things which i think she wouldnt suffer with so much if she had access to Kuvan.

Q8. If PKU people were giving Kuvan i dont think they would need extra help or support.

Q9. I think the whole process is unfair.they have not looked into everything with great detail.that fact they said it can be used until they turn 18 is confusing.it doesnt go away for its forever.no matter if they ate disadvantaged or not they all deserve to be treated fairly which is not the case here.

Q10. Everyone should have access to the drug.they all have the same condition so all should get it.

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 4

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. As a parent to a 7 month old boy with PKU, I viewed the new recommendations with mixed emotions. I wholeheartedly agree that Kuvan should be available to children, but it also must be available to those over the age of 18. As the recommendation stands, if my son responds to Kuvan, we will raise him on a less restrictive diet than he would otherwise be on. Whilst we will still have to count protein intake and plan meals, events such as parties, holidays and going to nursery will become much more possible. My son will learn about what he can and cannot eat as he gets older and grow accustomed to this way of eating.

What I cannot fathom, is how I explain to him, that on his 18th birthday, his supply of this life changing drug and his whole way of eating and living will be taken away from him. I must explain that the medical recommendation is that he must stay on diet for life, but at the same time it is not thought he would gain any benefit by continuing to take Kuvan. Both these positions cannot be true (especially when Kuvan is proven to show benefit for adults). It is either treatment for life or not.

At the age of 18 my son will likely be just about to take his A level examinations, and preparing to move away to university, enjoying all the freedoms (and risks) that late adolescence brings. How can he be expected to reach his potential whilst coming off a drug that not only increases dietary options, but also improves concentration, working memory, retention, mood and anxiety levels? How can I justify to my son that in the middle of the most important examinations of his life, he must risk severe cognitive effects, even if he manages to stick to the diet. How do I explain to him, that while he is attempting to manage his new found brain fog, his exams, and all the other challenges of late adolescence, he must also learn how to cook ultra low protein food, stop eating most of his favourite foods and become involved in the complex process of ordering and managing prescription foods for himself?

As a Clinical Psychologist with experience in Paediatrics, I am also gravely concerned that the timing of coming off this drug will coincide not only with personal transitions (university, adulthood, moving out) but also clinical transitions to an adult team. Much research points to the difficulties faced by children transitioning to adult services, in particular the reduction in attendance at appointments and many dropping out of contact with services all together (Johnston, 2006). This presents a substantial risk both enhancing the likelihood of coming off diet altogether and not having any medical monitoring or support, but also to individuals mental health. To be told your whole way of eating has to be severely restricted at a time your peers are gaining their independence will likely have a huge impact on the mental health of PKU young adults. Again, those lost to transition and not in touch with services risk isolation, depression, lack of support and for some severe mental health problems. My experience working with those with eating disorders also gives me cause for concern in terms of asking someone to overhaul their diet so completely. Humans are generally poor at sticking to diets, for a host of biopsychosocial reasons, and changing it this dramatically will surely cause an increase in both anorexia and bulimia and they struggle to manage food cravings, hunger, guilt and rigidity.

Reference
Johnston, P., et al. "Audit of young people with type 1 diabetes transferring from paediatric to adult diabetic services." Practical Diabetes International 23.3 (2006): 106-108.

Q3. NICE's statements are contradictory

Q4. Current evidence points not only to brain development continuing to the age of 25, but in face that it continues to change throughout adulthood (reference below). It would follow that brain damage could therefore occur at any age, and even if it looks different in adulthood, it may still be significant. It is reductionist to state that the adult with PKU's brain is not at risk of irreversible damage, not least because research has not been carried out in elderly PKU patients. History has taught us that the medical profession has time and time again failed to realise the significance of brain damage in older children, until it was too late for some. Please do not make the same mistake for generations of young adults.

Lebel, Catherine, and Christian Beaulieu. "Longitudinal development of human brain wiring continues from childhood into adulthood." Journal of Neuroscience 31.30 (2011): 10937-10947.

Q5. Even in the short time we have had our son, the impact on my husband and I has been significant. I had to stop breastfeeding which was something I had planned to do and wanted to do. Although guidelines state it is possible, the reality of expecting a week old baby to go between bottle and breast is just not an option for many and caused me significant stress and guilt.
Measuring exact amounts of two different formulas, including throughout the night, took a toll on my mental health and lead to me developing OCD symptoms, due to the catastrophic outcome that any mistakes would cause.
I have had to seek CBT on the NHS for the increase in my anxiety levels. Future worries remain, including those surrounding how my son will cope with transitioning to life without kuvan as a teenager.

Being a parent does not end at the age of 18 and my son will continue to need a high level of support, especially if kuvan is taken away from him.

It has also impacted how we will operate as a family. Before our child was born, we had planned for him to attend nursery 3 full days a week. The anxiety of someone else feeding him so much when the risk of brain damage from one mistake is too much. As a result, my husband and mother-in-law have had to significantly change their working patterns and reduce their hours by significantly more than originally planned in order to limit attendance to a nursery to two half days a week (which even for that we are very uncomfortable with, but a necessity in order to be able to pay the bills)

Q6. PKU not only involves parents, but also grandparents and other family members. We have had to spend a great deal of time explaining the diet to family, and even then there is only one other family member we can leave our son with over mealtimes as the diet is so complicated. We also worry about having a second child without PKU - the challenge of cooking for them and them having to face some restrictions (e.g. a vegetarian diet) for the sake of fairness.

Q7. I cannot comment from personal experience as my son is only 7 months. However I direct you to the research below which clearly supports the position that these effects continue into adulthood particularly in the area of sustained attention and mood. This effect is likely heightened as the diet itself requires a high level of sustained attention, and motivation (which is a component of mood). Therefore when adults are affected in this way, their adherence to diet is likely to drop, perpetuating a vicious cycle.

"High phenylalanine levels directly affect mood and sustained attention in adults with phenylketonuria: a randomised, double-blind, placebo-controlled, crossover trial." Journal of inherited metabolic disease 34.1 (2011): 165-171.

Q8. As a Clinical Psychologist, trained to Doctoral level in research, I would argue that quality of life can only be measured qualitatively not quantitatively, therefore it is a poor scientific argument that there is no evidence out there. I am aware that patient personal accounts were sent to NICE to be reviewed as part of the evidence. This is your evidence - read it.

Q9. I am gravely concerned that the guidance is not in accordance with equality policy or legislation. As a parent, I have already had to buy: a breadmaker, a food processer, an additional freezer, have an additional cupboard built to store PKU food and supplement, and an airfryer. We are fortunate to own a house where we can fit these additional items, and have the finances to afford them. I am concerned how parents would cope who live in a 1 bed flat, temporary accommodation, houses of multiple occupancy, or indeed adults in long term care facilities or prison.

The diet is incompatible and inaccessible for people with learning disabilities. I have a Doctorate and I still struggle.

Maternity is a protected characteristic and many PKU women are unable to plan to have a family because to do so means controlling their phe in an almost impossibly narrow range. May I also bring your attention to the mental health effects on a woman who is unable to control her phe in a narrow range, or has an unplanned pregnancy and therefore has a child with severe developmental delay. The subsequent guilt and shame she will feel, most likely for her entire life and that of the child, should land squarely at the feet of NICE reviewers who have it in their power to protect the future children of women with PKU but are wilfully choosing not to.

You mention cost effectiveness estimates - simply look at the cost of a child born with a learning disability (the outcome of an unplanned PKU pregnancy). I am sure these estimates are already out there and include medical appointments, Health and educational plans requiring additional support at school or specialist educational placements, lifelong access to carers.

Again, it is simply lazy and reckless to say the evidence is not there. This is a rare condition. Evidence must be sought from single case studies and from conditions with similar resulting needs.

Q10. NICE should recommend Kuvan to pregnant women. The evidence of disability to the child of poorly controlled phe is well documented and the evidence is there.

Q11. Maternity is a protected characteristic and women are being prevented from starting families by not having access to Kuvan.

Q12. As above, simply look at the costs of raising a child with a learning disability. These costs have surely already been calculated.

Q13. *[no response given to this question]*

Respondent 5

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I am a father to a 7 month old boy with classical PKU. He must adhere for life to a strict diet of 5g of protein a day in order to avoid brain damage.

I viewed the draft guidance at first with joy, but swiftly followed by anger. This looks like a token move to appease the campaign that has been ongoing to counter the injustice of not allowing access to a drug that is used in over 50 countries, including countries such as Romania and Syria.

I wholeheartedly agree that Kuvan should be available to children, but it also must be available to those over the age of 18. Should my son responds to Kuvan, we will raise him on a less restrictive diet than he would otherwise be on. We will still have to count his protein intake and plan meals but events such as parties, holidays and going to nursery will become much more possible. My son will learn about what he can and cannot eat as he gets older and grow accustomed to this way of eating, which is much more in line with 'normal'. The drug will also reduce the effects of any 'mistakes' (which of course happen - try avoiding 85% of food in a supermarket for life).

What I cannot even put into word, is how I explain to him, that on his 18th birthday, his supply of this life changing drug and his whole way of eating and living will be taken away from him.

I would then need to explain to him that the medical recommendation is that he must stay on diet for life as it is not thought he would gain any benefit by continuing to take Kuvan. Both these positions cannot be true (especially when Kuvan is proven to show benefit for adults). It is either treatment for life or not. The NHS currently recommends that the dietary treatment is for life. If a diet is needed for life to counter any ill effects in adulthood, then how come Kuvan is then stopped upon 18 years of age?

At the age of 18 my son will hopefully be just about to take his A level examinations, and preparing to move away to university, enjoying all the freedoms (and risks) that late adolescence brings. How can he be expected to reach his potential whilst coming off a drug that not only increases dietary options, but also improves concentration, working memory, retention, mood and anxiety levels?

Please tell me how I would explain to my son that in the middle of the most important examinations of his life, he must risk severe cognitive effects, even if he manages to stick to the diet? How do I explain to him, that while he is attempting to manage his new found brain damage, that he must also learn how to cook ultra low protein food, stop eating most of his favourite foods and become involved in the complex process of ordering and managing prescription foods for himself?

I am a sixth form college teacher. I am acutely aware of the difficulties that the teenage years represent. That alone scares me enough as a parent. Add on the fact that Kuvan would be snatched away from my son at 18 years old and he would then face depression, anxiety, brain fog and brain damage and it frankly terrifies me.

I can only think that this decision has been taken on purpose to limit drug access - i.e. to scare parents into not putting their children on Kuvan because of the future consequences of then taking the drug away.

Much research points to the difficulties faced by children transitioning to adult services, in particular the reduction in attendance at appointments and many dropping out of contact with services all together (Johnston, 2006). This presents a substantial risk both enhancing the likelihood of coming off diet altogether and not having any medical monitoring or support, but also to individuals mental health.

To be told your whole way of eating has to be severely restricted at a time your peers are gaining their independence will likely have a huge impact on the mental health of PKU young adults. Again, those lost to transition and not in touch with services risk isolation, depression, lack of support and for some severe mental health problems. My experience working with those with eating disorders also gives me cause for concern in terms of asking someone to overhaul their diet so completely. Humans are generally poor at sticking to diets, for a host of biopsychosocial reasons, and changing it this dramatically will surely cause an increase in both anorexia and bulimia and they struggle to manage food cravings, hunger, guilt and rigidity.

Reference
Johnston, P., et al. "Audit of young people with type 1 diabetes transferring from paediatric to adult diabetic services." Practical Diabetes International 23.3 (2006): 106-108.

Q3. NICE's statements are contradictory

Q4. A plethora of research demonstrates that brain development not only continues to the age of 25, but well beyond (reference below). It would follow that brain damage could therefore occur at any age, and even if it looks different in adulthood, it may still be significant. It is reductionist to state that the adult with PKU's brain is not at risk of irreversible damage, not least because research has not been carried out in elderly PKU patients. Newborn screening was only introduced in the 1950's/1960's. Before this time, those with PKU have severe brain damage.

History has taught us that the medical profession has time and time again failed to realise the significance of brain damage in older children, until it was too late for some. I beg that you do not make the same mistake for generations of young adults.

Lebel, Catherine, and Christian Beaulieu. "Longitudinal development of human brain wiring continues from childhood into adulthood." Journal of Neuroscience 31.30 (2011): 10937-10947.

Q5. Whilst our son is only 7 months old, the impact of my son's PKU diagnosis has been significant upon me and my wife.

Measuring exact amounts of two different formula milks (given we wanted to avoid the 'lottery' of breastmilk and not knowing precisely how much protein was being consumed), including throughout the night, took a toll on my wife's mental health. It lead to her developing severe OCD symptoms, due to the catastrophic outcome that any mistakes would cause to our son.

The burden that every meal, snack and drink you give to your child may give him brain damage is a heavy one to carry. I only hope this burden gets easier, or at least I develop coping strategies to better manage the burden.

Being a parent does not end at the age of 18 and my son will continue to need a high level of support, especially if Kuvan is taken away from him.

It has also impacted how we will operate as a family. Before our child was born, we had planned for him to attend nursery 3 full days a week. The anxiety of someone else feeding him so much when the risk of brain damage from one mistake is too much. As a result, my husband and mother-in-law have had to significantly change their working patterns and reduce their hours by significantly more than originally planned in order to limit attendance to a nursery to two half days a week (which even for that we are very uncomfortable with, but a necessity in order to be able to pay the bills)

Q6. PKU not only involves parents, but also grandparents and other family members.

We have had to spend a great deal of time explaining the diet to family, and even then there is only one other family member we can leave our son with over mealtimes as the diet is so complicated.

We also worry about having a second child. We have even considered adoption for a second child. It is a 1 in 4 chance of our second child having PKU. I already feel guilty at the thought of having another child and knowingly potentially 'giving' them PKU and consigning them to the life of avoiding 85% of supermarket food as well as all of the symptoms that NICE have written about, such as difficulty with focus, depression or anxiety, disordered eating, digestive problems, headaches, low mood and sadness, feeling tired all the time and being in a heightened emotional state (including aggressiveness, psychosis and paranoia).

Q7. I cannot comment from personal experience as my son is only 7 months. However I direct you to the research below which clearly supports the position that these effects continue into adulthood particularly in the area of sustained attention and mood. This effect is likely heightened as the diet itself requires a high level of sustained attention, and motivation (which is a component of mood). Therefore when adults are affected in this way, their adherence to diet is likely to drop, perpetuating a vicious cycle.

"High phenylalanine levels directly affect mood and sustained attention in adults with phenylketonuria: a randomised, double-blind, placebo-controlled, crossover trial." Journal of inherited metabolic disease 34.1 (2011): 165-171.

Q8. There is little quantitative evidence because it is a rare disease. There is qualitative evidence though - those with PKU and their families. Listen to us, please. Obesity costs the NHS £6bn a year. But we can't afford medication for a few thousand people.

Q9. I am concerned that the guidance is not in accordance with equality policy or legislation.

As a parent, I have already had to buy: a bread maker, a food processer, an additional freezer, have an additional cupboard built to store PKU food and supplement, and an airfryer. We are fortunate to own a house where we can fit these additional items, and have the finances to afford them.

I am concerned how parents would cope who live in a 1 bed flat, temporary accommodation, houses of multiple occupancy, or indeed adults in long term care facilities or prison.

The diet is incompatible and inaccessible for people with learning disabilities. I have a postgraduate university degree and still struggle at times with calculating the protein intakes based on nutritional information contained on food packaging.

Maternity is a protected characteristic and many PKU women are unable to plan to have a family because to do so means controlling their phenylalanine in an almost impossibly narrow range. May I also bring your attention to the mental health effects on a woman who is unable to control her phenylalanine in a narrow range, or has an unplanned pregnancy and therefore has a child with severe developmental delay. The subsequent guilt and shame she will feel, most likely for her entire life and that of the child, should land squarely at the feet of NICE reviewers who have it in their power to protect the future children of women with PKU but are wilfully choosing not to.

You mention cost effectiveness estimates - simply look at the cost of a child born with a learning disability (the outcome of an unplanned PKU pregnancy). I am sure these estimates are already out there and include medical appointments, Health and educational plans requiring additional support at school or specialist educational placements, lifelong access to carers.

Again, it is simply lazy and reckless to say the evidence is not there. This is a rare condition. Evidence must be sought qualitatively and from conditions with similar resulting needs.

Q10. *[no response given to this question]*

Q11. NICE should recommend Kuvan to pregnant women. The evidence of disability to the child of poorly controlled phenylalanine levels is well documented and the evidence is there.

Q12. *[no response given to this question]*

Q13. Draft guidance says “a dose of up to 10 mg/kg is used”. This cap should not be in place. Clinicians should have the flexibility to prescribe the dosage according to individual patient needs and in line with the manufacturers authorisation which ranges from 5mg/kg to 20mg/kg. With this current guidance, there is a large risk that many patients would be classified as non-responders, when they in fact need the higher dose of 20mg/kg. This is the common practice in other countries. The costing against 10mg/kg is appropriate as that is likely to be the average dose, but clinicians need the flexibility to prescribe up to 20mg/kg where required.

Respondent 6

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. My son is 19 months old which would mean him taking Kuvan for the next 16 1/2 years to then have this taken away will be a hard go him as a young adult and us as parents, his brain is still developing and the risk of him coming off diet completely is a big issue for us. Taking a drug all of your life to have it removed is not only risking his physical health but his mental health too

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. Yes, these comments are true.

Q6. Yes, both mine and my husband parents do not feel comfortable looking after our son as they feel too much pressure to get it right.

Q7. Yes. My son has frequent chest infection, when he has one his phenylalanine levels rise. We have also started to see how different his mood/behaviour is when he has high levels

Q8. *[no response given to this question]*

Q9. How can you put a price on someone's life. Food is a basic human right and people with PKU are extremely limited to what they can have

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 7

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Immediately phasing out Kuvan so that 18 year olds suddenly need to go from completely normal to following a very strict and high stakes diet is extremely unrealistic, and will likely cause long term harm. 18 is a uniquely bad time too, since the majority of 18 year olds are already going through massive lifestyle changes like leaving school into a first job or moving away from home. Some treatments may even stop during exam periods or other edge cases like pregnancies, which is likely to cause even more harm.

I think supplying Kuvan universally is the most sensible option, as it will lead to massively improved lifestyle for everyone. But if the proposal insists on not supplying Kuvan, it makes a lot more sense to prescribe post 18 on a case by case basis, or slowly phase out treatment as opposed to stopping at 18.

Q3. NICE's statements are contradictory

Q4. I do not have any personal, however based on forums and Facebook group there appears to be a large %age of people out there with experience.

Q5. Absolutely, not only would Kuvan improve the lives of people with PKU, It would also improve the lives of their family and carers. Additionally, it is likely reduce the economic impact of the low protein diet on PKU families, as while many foods are provided as part of the NHS care, a lot of standard market food is needed too, which is often more expensive than traditional alternatives as they usually fall under niche groups.

I also think that it is key to add: care does not magically stop at 18 years old. Many PKU carers and families continue to help their children for a very long time after 18, and while many 18 year olds immediately become independent, and may be independent according to law, reality is a lot more complicated than this.

Q6. Yes, every single PKU person I have met has a parent who has left full time work during the process of caring. Whilst they may be able to continue full time work when that child turns 18, it is not that simple, and having left work for many years they often struggle to reenter the workplace, and if they find work they often reenter at a massively reduced salary. The economic benefit here should consider every stakeholder, not just the individual with PKU.

Q7. Yes I have, my additional comment would be that everyone (including NICE and doctors) knows that literally none of this goes away when you turn 18.

Q8. This is absolutely true, none of this will be a factor if Kuvan is provided universally.

Q9. Nothing is considered fairly, some people may find the diet easy, others may not. With the clear success of Kuvan, it's obvious the diet is now obsolete.

Q10. Kuvan should be provided to pregnant women, this recommendation from NICE does not line up with the NHS's own treatment of pregnant women with PKU which is enhanced diet control to prevent harm to the unborn child. I don't mean to be unprofessional, but this is obvious stuff.

Q11. I do not have any evidence, I am an IT support engineer not a medical professional.

Q12. No comment, just that I completely agree with this statement.

Q13. No additional comments.

Respondent 8

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I think it is completely wrong to take away a life changing drug as soon as a child turns 18.
I do not know of any other medication that is given for a lifelong illness that is suddenly taken away. How can a child be expected to go from living a relatively normal life and then suddenly have to change everything about their diet and lifestyle over night.

Growing up with PKU was so extremely difficult for me. I would hide my lunch from my friend's at school because I was so embarrassed of the way the low protein food looked.
I ended up having such a bad relationship with food and developing an eating disorder.
It caused me to have serve depression during high school, I was tired all the time and felt like I always had brain fog.

If kuvan was provided for me who knows how different my life could have been. It is not fair to delay this drug to both children and adults and give them an opportunity to live their best life.

People moan about going on a diet before a holiday etc.
Imagine having to be on a severely restricted diet your whole life and knowing if you did not follow it you could end up with brain damage.

As a child growing up I wished everyday that there would be a cure for PKU and it is a wish I still have as an adult. It is the most frustrating thing in the world to know that there is this proven, life changing drug that so many other countries provide for people with PKU and yet the UK have turned a blind eye to it for 12 years.

Q3. I do not agree with NICE's view

Q4. My brother and I both have PKU. We try our hardest to stick to the diet however it is extremely difficult to keep levels in a safe range. When our level are high it changes everything about us. We become depressed, constantly tired, unable to think clearly. It is not just us that notices this but also friends and family. To say high levels don't effect adults is completely wrong.

Q5. My poor mum and dad had to constantly explain to school, family's friends what my brother and I could/could not eat. Every single thing we ate was weighed so we were getting the exact amount of protein we were allowed to have.
I didn't have my first bite of chocolate until I was 7 years old and my parents were so happy for me that they even recorded it.
It was very difficult for my parents having to cook separate meals all the time and to make sure we had our supplements even though they taste absolutely horrendous.
When I went to school camp my mum had to cook me a whole weeks worth of food of which I was so embarrassed about when it all got loaded onto the bus with everyone asking, "Why have you got special food?"

If kuvan was available growing up it would not have just changed mine and my brothers life but also my whole families life too.

Q6. Pku has a huge affect on the whole family.
My sister wouldn't be allowed to certain treats in front of me so I wouldn't get upset about not being allowed it. As I mentioned above my parents had to cook different meals to what the rest of the family were eating. A lot of the time growing up we never went to restaurants because the only thing my brother and I could really eat was chips.
Going on holiday was a nightmare with all the supplements and food we had to pack.
Food is a constant in everyone's life there PKU is as well.

Q7. I agree 100% with this. Literally everything stated above is sadly relatable to me. I can tell when my levels are high without even doing a blood test because I feel so extremely anxious that I have panic attacks.
I have struggled with depression since I was a teenager. (Especially as a teen as I found it very difficult to control my diet)
It resulted in me missing school, losing friends and feeling that I was a failure.

I would love to know what it is like to feel 'normal' and the fact that there is a drug that could allow me to feel that way is so exciting.

That is why I find it completely unbelievable that it is still not available on the NHS. It is provided in so many other countries with patients saying how much their life has changed for the better.
Why is the UK not doing the right thing and allowing people with PKU the chance of a better life.

I just wish whoever reads this can try to understand how frustrated we all are. Imagine if it was you in this position or your child.
To know there is a "wonder drug" out there and be denied the chance of taking it is heartbreaking.

Q8. *[no response given to this question]*

Q9. The NHS spends an insane amount on alcohol and drug abuse and even obesity. All things that people have done to themselves and have control over. Having PKU is not something we have done to ourselves. It is something we were born with and will have to live with for the rest of our lives.
The fact that Kuvan can make PKU actually manageable and isn't available on the NHS due to "costs" is completely unfair.

Q10. I am 30 years old and would love to have children. I am however petrified of giving my baby brain damage due to not being able to control my diet. Sometimes even when you are on the strictest of diets your levels can shoot up due to something as little as having a cold.
I am very aware of the levels my bloods need to be in order to keep my baby safe. What scares me is that I have not been under that level (even when trying extremely hard) in my whole life. So how am I going to do it for 9 months.
Kuvan would allow me have a pregnancy that is more normal without the complete stress of worrying about every single thing I eat.

Q11. See above. It is unethical to knowingly keep a drug that can prevent brain damage to an unborn baby not available to those who need it.

Q12. The cost of the NHS looking after a baby with brain damage for their whole life must be more expensive than providing Kuvan to avoid that happening

Q13. Please please please provide Kuvan to ALL those with PKU. It should have been available 12 years ago but now there is a chance to allow people in the UK the same chance of a better life as all those who have access to the drug around the world.

Respondent 9

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. It seems unfair to provide medication which has a positive affect on a child, but cannot have a similar effect on an adult. Young adults especially.

Q3. NICE's statements are contradictory

Q4. No i am a Father of 2 children with PKU, when their levels are high they can act in a negative way.

Q5. Totally agree also struggle with a diverse diet.

Q6. I agree family carers are also affected.

Q7. I agree.

Q8. I have a nephew who does not have PKU. He is able to manage his life a lot more easily.

Q9. This should not be about cost but about patient care. Also the more widely Kuvan gets used there should be a reduction in cost.

Q10. Please look at this carefully, i have a daughter and she may wish to become a parent in future.

Q11. N/A

Q12. If Kuvan can prevent metabolic issues with unborn children thats good.

Q13. Please consider making this available for all adults and children with PKU throughut England & Wales.

Respondent 10

Q1.I do not agree with stopping access to Kuvan at age 18.

Q2. This is the wrong decision. How unfair is it to take a child off a severely restricted diet, more freedom to eat more protein, open them up to all these new products, tastes and textures then at the age of 18 tell them that it you can't eat them foods anymore and you have to cut your protein intake on half for example! This is sending the wrong message to our PKU children. We cannot swap and change their lifestyle like this! There will be damage from 18 upwards if the teenager us unable to go back to their old diet. Mental Health is a huge factor, there are lots of reports I have read where adults are affected by coming off diet. Brain fog, difficulty concentrating to name a few. I want my 18 year old to live a happy healthy live and chase her dreams, not to be held back by this horrible condition! Please help us

Q3. I do not agree with NICE's view

Q4. My daughter is currently 10 so I dont have first hand experience of PKU in adult hood but have read and spoken to adults with PKU that are unable to follow their strict diet and how this has definately affected them. Brain fog, depression, lack of concentration etc.

Q5. I am a single mum with a PKU child. PKU has taken over my life! I have to count protein exchanges and check the ingredients of everything my child eats day in day out. I have to remember her supplements every 6 hours. We can't ever get up and go, we always have t plan meals. Mt daughter is upset regular because she can't try the same things her friends have. She can't have a hot dinner in school, she can't have chocolates the teachers or other children take in for birthdays. Its so upsetting, more upsetting to know there is help available with Kuvan and people are fighting against giving this to us! I can only work a small number of hours as I cannot just leave my child with other people, they don't have the knowledge about PKU. She can't have sleepovers like normal children. Holidays are stressful with her diet! I worry from 18 onwards when she should be chasing her dreams/career paths that she will not cope and I will have to always help her manage diet. Kuvan would help us both hugely.
I also worry that my daughter may become pregnant and diet would be extremelly difficult to deal with in this case, Kuvan would be help massively with this.

Q6. Yes this should be taken into account. They don't live in the life of a PKU family. I have to buy special foods all the time that have low protein and no aspartame, we can't just order a takeaway for treat night. I have to cut my hours at work down to be able to be there for my daughter before and after school to help manage meals and supplements. I feel my child misses out on so much, easter eggs, christmas dinners, school dinner with friends, sleepovers, holidays etc. I rent and have to ensure that I have a place with space to because store her medication, food products, bread makers etc This takes up my entire spare room. I should only need to rent a 2 bedroom property but have to pay for 3 bedrooms to have the space.

Q7. agree, it definately has a huge inpace on mood. Every day having to be severley restricted on what you can eat is a huge burden to carry. There is never a day off! I have to take food and sweets away from her and this is so upsetting for both of us. I would love her to have a normal life and feel the same as her friends. She goes to Brownies and has to miss out on cooking days and camping weekends because of her diet. I don;t want her to feel dofferent from other people. She is excluded a lot because of PKU

Q8. Its is so difficult for both me and my child to deal with KU. Its 24/7, there is no break. Neither of us can live a normal life because of it. I am constantly worrying about her health. She can't just go into a shop like her friends and pick up a packet of crisps or bag of sweets. Imagine that!! Imagine going to the park on a summers day, all the other children are queueing for the ice cream van and I have to tell my daughter no!!

Unless you have lived with PKU you don't realise how important and what a big part of your life revolves around food.

Q9. PKU can be a huge issue during pregnancy and may prevent individuals from wanting to have children because of this. This should not be with way. I definetly find it difficult being a single parent working part time dealing with the cost of the special foods. Its hugely time consuming as well so I worry if I worked more hours her diet would slip

Q10. It should definetely be available for pregnant woman as I have mentioned before. A normal pregnancy is scary enough and difficult to deal with at times so having PKU and being pregnant is an even greater worry! Kuvan should be available to help mothers throughout his without such a burden worry

Q11. No eveiden but agree this should be given to woman for this reason

Q12. *[no response given to this question]*

Q13. I really hope they will take on board the comments from parents like me dealing with brining up PKU children. I worry all the time about my daughters help, and worry that when she becomes a teenager her diet will become even more difficult to control. She will want independence and will want to do normal things teenagers do. PKU holds her back from doing normal things. Please help us help them

Respondent 11

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I find it perplexing a child can take life saving / supporting medication, and then have to stop at an arbitrary date , which will negatively impact how they live their life from that point on. Maturing from a child to an adult is not a point in time on the 18th birthday, there is some much more that occurs from 18 on, especially when factoring in how a young adult has to look after themselves when living on their own for the first time (eg university).

Q3. I do not agree with NICE's view

Q4. I have zero faith in that there will be zero brain damage in an over 18 as a result of high Phe levels. Why run the risk of this on the body’s most important organ.

Q5. 100% agree. To add. PKU also affects friendships , as a PKU child needs to be aware of things they can’t have vs their peers. This introduces significant difficulties when eating out at pubs, restaurants; when they go and have tea at a friends, where there is party food at friends birthday parties; if we go out for lunch as a family, it’s all tremendously difficult to find low protein foods.

Q6. Yes. Immediate family; affect on siblings , on family careers eg grandparents etc and the fact that non prescription low protein foods are significantly more expensive eg cheeses

Q7. Yes, we have experienced all of the above and continue to do so

Q8. We struggle with family out for lunch or dinner due to finding suitable restaurant menus. Italian is out - pizza / pasta is a no go. Veggie lasagna, no go. Nut roast, no go. We rely heavily on the metabolic team for advice and support, and so does our child as conversations with this team help them contextualise their problems , provide them with some ideas and support and ultimately give them a bit of confidence

Q9. No.

Q10. Provide kuvan as an option for the mother to be.

Q11. Agree.

Q12. Seems to be a missing data point.

Q13. Not fully thought through, half baked. should provide Kuvan over the age of 18.

Respondent 12

Q1.I do not agree with stopping access to Kuvan at age 18.

Q2. If at 18 Kuvan stopped in my opinion it would cause considerable difficulties for my young son who is now aged 13 as he would experience new freedoms with Kuvan but then having to completely revert back to his restricted and very limited diet. An example of this is if my son went on to further education living away from home he would have to manage his own diet which would be considerably difficult due to the removal of Kuvan and having to re-educate himself on a drastically restricted diet.

Q3. NICE's statements are contradictory

Q4. none

Q5. Having 13 years experience I would relate strongly to all the above issues

- not able to allow him the freedom of staying away from home without a parent/carer i.e. school trips/activities, sleepovers with friends, difficulties in holiday arrangements/flights.
- as a parent I spend considerable time sourcing supermarkets, specialist shop and online to identify suitable/safe food products to enable him to have a more varied diet this can also be a costly exercise and restricts my hours of work considerably.
- during the last 13 years I am constantly informing schools, friends, outside activities about his condition. In circumstances when he is attending parties to explain how he is not able to partake in any of the foods on offer but must take his own "packup". Educating my son that

when away from me/home he must not accept any food or drinks without guidance.

For my son, for the rest of his life, not just the next 5 years to be able to lead a more normal lifestyle would be a most momentous and rewarding outcome.

Q6. Any economic issues are in our circumstances covered by his parents.

Q7. We have experienced all of the above and more which makes a "normal" family life difficult anything that can be provided to help manage or alleviate some of the issues would assist him, other members of the family and external issues outside of the home.

Q8. Apart from extra support at school involving one to one tuition and one to one supervision at meal times whilst at school.

Q9. No - Equality is about treating all people the same particularly in respect of health, all people whatever their issues or background should be treated the same.

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 13

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. From diagnosis, we have always been told that the treatment for PKU is a 'diet for life'. At no point has it ever been considered, in our household, that our daughter would abandon treatment of her condition upon reaching adulthood. Whilst we welcome the recommendation that Kuvan should be offered to children, I think it's a unacceptable that the treatment would then be removed at age 18. At that age, young people are learning to manage dietary treatment on their own, they may be going away to university or looking for work- this is already enough pressure, without the sudden removal of treatment that they've been relying on to manage their metabolic condition. The effort required to effectively manage your PKU should not be underestimated. I believe that anybody with PKU who responds to kuvan should be able to use this medicine, regardless of age.

Q3. NICE's statements are contradictory

Q4. I do not feel NICE have placed significant enough importance on understanding and considering the long term effects on the brain relating to dietary management of PKU

Q5. Yes I agree. As a parent of a child with PKU, managing the condition is a constant struggle and a large source of anxiety. Every meal or item of food every day has to be carefully thought out and there is no flexibility within the diet. You don't get a day off.

Q6. Yes. Parents of children with PKU are ultimately responsible the care and diet of the child. To overlook the sacrifices they make to accommodate such a strict diet is wrong.

Q7. Yes I agree. My daughter has experienced low mood due to her PKU when her blood phe level is out of range (the increased blood phe resulting from illness or periods of rapid growth, NOT bad management of the diet). She also has trouble with her ability to focus, her recall and her attention also due to elevated blood phe levels. My daughter also often experiences digestive issues as a result of her dietary requirements, resulting in discomfort and pain. She has been sent home from school due to PKU related stomach issues that the school have assumed are due to stomach bugs.

Q8. Further evidence needs to be gathered before this subject can be considered accurately

Q9. No, I do not think that NICE has properly considered treating people fairly. Someone with learning difficulties, for example, may struggle to understand nutritional information. If English is not your first language, then accessing advice may be difficult. Those suffering with autism may struggle to understand the complexities of their diet. The PKU diet is complex, even for someone who doesn't face these issues.

Q10. Kuvan should be made available to all pregnant women to help them manage their Phe levels during pregnancy, therefore mitigating effects on the unborn child.

Q11. It is well documented that poor phe control has devastating effects on unborn children

Q12. It is unfair not to consider the ramifications on an unborn child in the long term.

Q13. The recommendation of 10 mg per kg should be reconsidered. For some people a dose this high would not be necessary, for others would be too low. The recommendation for allow for a range of possible doses. The extra cost of people using higher doses would be balanced by the patients on lower doses.

Respondent 14

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. My son who has PKU is 13 and my daughter who has PKU is 7. At the moment my wife undertakes everything pertaining to their diet. However we are starting to encourage our son to be more responsible for his diet and exchanges. The fact he will have access to Kuvan and then have it taken away in 4/5 years is unfathomable. The diet is so hard to maintain and follow, to then have something that may make their lives slightly more tolerable taken away to me is beyond comprehension. The sacrifices that my two children make to follow their diet is far

beyond anyone who isn't a PKU sufferer could ever understand. This stage of my sons life is a particularly difficult stage to negotiate for any teenager, but to have something that may make his life that bit easier and then have it taken away will in my opinion only lead to long term lasting issues. These issues could be damaging mentally, physically and emotionally and will probably cost the health service more in the long run.

Q3. I do not agree with NICE's view

Q4. I cant speak on this subject with any authority as both my PKU sufferers are children, but as you would expect from any parent of a PKU sufferer we have researched what happens in adulthood and have heard many experiences from the fantastic PKU community we are a part of. The fact that NICE only refer to brain damage and none of the other associated side effects of the PKU diet worries me. Surely the current focus around Mental Health and depression needs to be considered among the PKU adult community and the effect this would have on not only the sufferers but the wider health service in general.

Q5. A valid question for NICE: "does anyone on the panel that have made this judgement live with anyone with PKU?" I don't mean that rudely but the sacrifices my wife makes for our two PKU sufferers is immeasurable. Our lives have been totally changed forever with our two but we wouldn't have it any other way. The effect the diet has on not only my two children but also my wife's life is difficult to sum up in a sentence but to say from the moment you wake up to the moment you go to sleep your day is dictated by the diet, wouldn't be far from the truth. My wife only works part time so we can manage everything our two's diet. The extra baking / Cooking required would be comparable to what would be required for a restaurant!! Some evening 3/ 4 different meals are prepared based on age differences. My other concern with this statement is that does the panel think we cut off all communication and support when the kids reach 18. My future 18 year old son who maybe at university wouldn't get any support from his family around his diet??

Q6. We are fortunate that we have the support of our in laws about 5 mins away. To say that the Mother in laws life is consumed by reading labels and protein contents of products would be an understatement. My mother in law used to have her own catering business so is used to cooking and preparing meals but the food she prepares for our 2 is something that has always been hard for her and my wife alike. The time it takes to source correct ingredients to then weigh out and ensure you are cooking correctly, because lets be honest even a dish as simple as PKU pasta needs to be cooked slightly differently to normal pasta, and if you need to ask me why, you have no understanding of the type of food the PKU community eat. I am also a little concerned by the statement "to value how much Kuvan was worth".... This is a potentially life changing drug for the PKU community, are we putting a value on someone's life now? I don't think we can honestly put a value on the emotional impact on my wife's life this diet has as well. We have attended numerous kids parties where our two have had to have a completely different meal and my wife has come home in tears. At the moment my son is having counselling sessions around his relationship with food as he is now at secondary school and walking to school with friends, they are visiting shops and buying what they like and eating it, my son really struggles with this and the counselling is providing him with ways to deal with this and strategies to cope and feel as though he is a normal teenager.

Q7. I agree with and have seen all of the above symptoms, imagine having all of them at the same time as well!! My biggest issue though is the mental health timebomb we have ticking here. As an example my son and daughter suffer from all of the above symptoms and in my limited knowledge the Kuvan will help control these to an extent which is fantastic, imagine someone's mental state when at 18 you say: "off you go you have to deal with all those issues your self now" without any help. At the very least I would expect them to be on anti depressants, that's before something even stronger. Then what about the knock on effect on family life when I have my son who is refused access to a drug because of his age but his younger sister with the same condition still has access to it. What's going on in my daughters mind as she prepares to approach 18, hardly something to look forward to at an already challenging time in their lives.

Q8. My daughter currently receives extra help at school with reading and writing, I have no idea of the cost of it but I cant imagine its cheap! This will only get worse the older she gets as school will have to provide T/A's / learning support to ensure that she remains at a level relevant to her age. As previously mentioned my son is currently under the treatment of a psychologist from St Thomas's following a referral from the dietary team. we have also had to have extra tuition for him from his primary school and he is under monitor at secondary school.

Q9. In my opinion I don't think it matters what your situation is, if you suffer from PKU you should be considered for the treatment of Kuvan end of. This applies to children , adults, pensioners whatever age you are. So what is being said here is that because it couldn't quantify the effect it would have in adults its best not to give it to them, I am shocked and saddened by a statement like that from a 1st world country like ours.

Q10. My limited experience of reading about this scenario is that not only is it hard to manage your diet for yourself to do it when you are expecting a child must be beyond difficult and absolutely petrifying. In years to come I hope to be in this scenario with our daughter but the thought that she would get no support from a product that is available and helps is beyond my comprehension. It must be offered to women who are expecting as the ability to consume more natural protein must be beneficial for the newborn baby. This has been "modellled" in non PKU sufferers quite easily.

Q11. Not at the moment but hopefully in a few years time.

Q12. How can you put a cost on that?? But surely it needs to be considered even if for the preventative measures it will provide.

Q13. My overriding fear is the lasting mental health effect this will have on the whole PKU community. We will have children who will have access to this fantastic drug that greatly enhances their life and makes a wholly difficult condition a bit more bearable and then have it removed. At the other end of the spectrum will be the adults who have a constant daily struggle to live a normal life denied the opportunity to make life a bit more bearable. I only hope and pray that this decision is reviewed and considered on the importance it requires. I hope this has been of use and I look forward to hearing the outcome.

Respondent 15

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. PKU effects both children and adults with PKU. The fact that NICE are recommending that it should stop being provided at age 18 is an extreme worry. The brain does not stop developing until around 25 year of age; for some, this may not be until they are 30 years old.
My son is currently 16.5 years old. He has PKU. He has an extremely difficult time adhering to diet. Should he be receptive to Kuvan and he started taking it, under NICEs current recommendations, he would only have it for around one year! Would I put him through this? No I would

not. It would be inhumane to start and then stop him taking it. What other drugs are stopped at 18 in the UK? I do not believe there are any in the UK that are stopped at 18 years of age, if they are proven to work for both children and adults!

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. Anyone that is 18 years of age has a long way to go before their brain has fully stopped developing. It has been found that non-compliance of diet tends to increase as children enter adolescence, and nearly one in three children at ten years old have blood phe levels above the recommended range (MacDonald et al., 2010; Blau et al., 2010). Adolescence is a period of significant physical, hormonal, and neurochemical change and takes place between the ages of 11 and 25 years of age (Colver & Longwell, 2013; Lebel & Beaulieu, 2011). This can be an exceptionally testing period in which to remain on diet and clinical health care service provision could be provided to assist in this challenging transitional phase of development. This means that children, young people and adults with PKU should be provided with support in this matter. I consider that any individual with PKU, that was receptive to Kuvan, should be prescribed this throughout their life to fully support them in this challenging disorder.

Q5. As a carer of a young person with PKU, I can acknowledge that this places a great deal of strain on you as a person. There is the ever present risk of having high blood Phenylalanine (Phe) levels. The fear that this provides is immense at times. I gave up full time work to manage my child's care when he started school. I found it too challenging and needed to prioritise my son in preparing his diet, cooking food constantly from the prescription food provided, ordering prescription food, which at times was not easy to get hold of, and concern felt that as I was not with him at school, he may eat something that caused his blood Phe to rise. The latter occurs on numerous occasion's as school cannot provide one on one support for him in their environment. This has caused a very real high level of stress for me and I have became quite ill at times. Going part-time at work was the only feasible response to this situation. The extra time burden has been calculated as of >19.3 hours per week (range 0 - 79 hours per week; median 3 hours per day) in managing the extent of the diet (McDonald et al., 2016). I would very much welcome a form of medication, like Kuvan, for my son; should he be receptive to it. This would potentially allow him more freedom with his diet, less chance of brain damage, and a better quality of life all round. It would also help me to be less worried about him and to feel more confident that his PKU would not cause him irreversible brain damage and issues throughout life.

Q6. PKU does not only affect the individual that has it, but parents, other siblings, along with grandparents and extended family members; included in this friends of the family. Concern is felt on an ongoing basis surrounding high blood Phe levels. Worry is voiced about how the young person can maintain their diet when there are so many 'temptations' for them to 'cheat on diet' and eat high protein foods; this is especially true for adolescents. In conjunction, extended family members worry about what the PKU child/young person can eat when in their presence when at a family gathering. As NICE may be aware, the diet is extremely restrictive, very difficult to manage and causes considerable challenge for all members of the family. Should by son be receptive to Kuvan, I know that all family members would breath a sigh of relief for him. With this, it would lower all family members concern about him 'sticking to diet' and not becoming brain damaged, or having other neurocognitive function issues throughout his life.

Q7. Although the low protein diet assists to an extent in averting permanent neurological damage, there continues to be an element of negative neurocognitive effect for a significant proportion of people with treated PKU (Bilder et al., 2016). There is a propensity during adolescence to have uncontrolled and raised blood phe (Guest et al., 2013). As such, individuals with treated PKU can have cognitive deficits, learning difficulties, and emotional problems at significantly higher rates than in the general population per se (Waisbren & White, 2010). PKU and attention deficit hyperactivity disorder (ADHD) have similar overlapping phenotypes, which detail dopamine dysregulation and executive functioning deficits along with white matter pathology. In tandem, both have hypoactivity of behavioural inhibition systems, although, whilst having similarities the disorders are not the same (Christ et al., 2010; Anderson & Leuzzi, 2010). However, and conversely, ADHD occurs approximately at twice the rate of the general population for those with PKU (Stevenson & McNaughton, 2013).
My son is diagnosed with ADHD and PKU. PKU and ADHD have an extremely debilitating impact on him. Should his Phe levels rise through cheating on diet and eating high protein food, a vicious circle is experienced. Should he have high levels of Phe, he may then not be able to manage his diet and medication tasks for both PKU and ADHD, along the lines of executive functioning issues; this unavoidably creates more Phe as he will then not prioritise his diet and then eat the wrong food, resulting in further neurocognitive functioning issues.

Q8. My son has a poor short-term memory. This can make him forget things easily. He is unable to follow direction, unless given as one instruction at a time. This puts extra strain on parenting him. He finds it difficult to tell you how he's feeling and gets confused about his social and emotional needs. This is compounded should he not take, or refuses to take his ADHD medication. Should his blood Phe levels also be too high due to his PKU he can present with a multitude of difficulties in his daily life. This is ongoing and takes places 24/7. Historically, my son has had respite care provided through Social Services. I did not pay for this as it was deemed to be a service he required. In school, my son has an Individual Education Plan, to support him in school with multiple issues concerning learning. Numerous extra costs have been incurred by the Local Authority, Care and Education owing to my sons PKU and ADHD. One compounds the other and vice versa.

Q9. Having PKU, in essence is 'not fair'. I do not consider that NICE has fully explored the fact that PKU impacts on both children and adults, having a son that is 16.5 years of age, along with having ADHD is extremely difficult to manage. Why does NICE think it would not be 'cost effective' in adults? Moving through adolescence with both PKU and ADHD is extremely challenging. So, in this sense NICE has not considered people equitably across the board irrespective of age.

Q10. NICE should fully recommend the use of Kuvan in pregnancy, owing to the very real risk to the unborn foetus. Numerous studies are available that quantify this risk. Why have NICE not explored this and apparently done only 'half a job' at looking at the evidence available?

Q11. Women with PKU may be concerned about having children of their own. In all senses, this is a very real risk. This would be owing to the increased risk during pregnancy of them having high Phe levels, which could then go to them having a child born with disabilities.

Q12. NICE need to look into the scientific research around this topic. There is a lot of research out there, so why haven't they looked at this? What is their excuse and reasoning behind it? My understanding is that NICE is an acronym for National Institute for Health and Care Excellence; from where I'm standing, I do not believe that they have completed a fully evidenced based piece of research surrounding the use of Kuvan in BOTH adults and children! KUVAN needs to be provided to both children and adults with PKU to support the numerous and differing impact that PKU has on the person.

Q13. No further comments.

Respondent 16

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. It seems crazy to allow children and young adults access to a medication that could literally be life changing - and not just with regards to the food on their plate. But then when they reach independence it gets taken away. How does that make any sense. Kuvan can help with cognitive ability, mental health and increase the allowed amount of protein a person can eat. PKU is a life long condition anyone who responds should be allowed life long medication.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. Having a child with PKU is a 24 hr job & the worry never leaves. We have no where in the world we can leave our daughter without weighed out food, instructions & what to do if she doesn't eat the required 'exchanges'. Along with leaving supplements that are vile to taste & regulary make my daughter gag & physically be sick, giving this responsibility to others is sometimes just to much. So as you can imagine it effects us socially, eating out is difficult & holidays are challenging. Life with Pku also comes with other challenges. My daughter is 6 and she struggles with her concentration at school, her ability to learn is possibly effected, however as her blood levels are well controlled we don't know if this is Pku related or just typical of a 6 year old. Patients lucky enough to take kuvan have reported massive improvement cognitively.
She is also becoming very aware that her bowel movements are different to her school friends & that when she goes she also smells different. (Due to supplements) Recently she gave herself tummy pains to the point of tears at school simply because she didn't want to go...but she refused to tell anyone what was wrong and why she had tummy ache. A problem I only see getting worse as she gets older. Kuvan could result in less synthetic protein supplements & more normal food which would in turn result in more normal bowel movements.
I could literally write an essay.

Q6. Yes of course it should be taken into account. Like mentioned above we really don't have much help and support due to the condition.

Q7. As mentioned above, school could be a whole new experience for my daughter if she had access to kuvan. Improved concentration, improved focus & improved energy levels could mean she has a very different educational experience and outcome to now.

Q8. More research is required my daughter struggles at school but we also have no evidence it is Pku related - although we believe it is.

Q9. The decision does not seem to fair me & in particular with regards to women wanting to conceive.

Q10. I know a lady locally who has a child with several serious issues due to uncontrolled phe levels while pregnant.

Q11. Use of kuvan while planning a pregnancy should be a given

Q12. *[no response given to this question]*

Q13. It is known that people respond to kuvan between 10-20mg dose. With this is mind knowing that already the response rate is about 30% only offering 10mg as a maximum dose is surly going to reduce the response rate even further? Kuvan should be trialed over a month minimum slowing people up to the 20mg maximum dose so that every Pku patient has a fair chance at responding to a life changing medication.

Respondent 17

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. To give a child a life changing drug and then to take it back off them is inhumane

Q3. NICE's statements are contradictory

Q4. Brain development and growth in
Education of the mind is a life long process

Q5. No where you can Leave a child with PKU as it's not recognised enough

Q6. Yes they should take it into account,

Q7. Ive seen with my 6 year old niece that she has difficult with staying focused, gets tired, gets anxiety with her supplements

Q8. My sister stopped working to look after her child

Q9. No

Q10. Kuvan should as standard be offered to women with PKU trying to conceive to ensure the health of the unborn baby

Q11. Know of a girl with PKU who had a child who is physically and mentally disabled

Q12. How can anyone put a cost on that

Q13. This drug should be rolled out for life.

Recommended dosage of 10mg isn't efficient enough to get a good response

Up dosage to 20mg

Respondent 18

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I would think that stopping the treatment at 18 could honestly be considered cruel. Having a 6 year old daughter with PKU and living her day to day struggles with her, the thought of taking most or all of her worries back only to then go back to square one doesn't bare thinking about.

Q3. NICE's statements are contradictory

Q4. Only from the many people we have spoken to within PKU groups who will attest to many issues in adulthood. The two statements NICE have made are totally contradictory and are frankly confusing.

Q5. 100% agree with the above.
Myself and my wife have had a lot of anxiety over our daughters condition. Her levels, aches and pains, toilet troubles, trying to swallow foul tasting supplements, blood testing and a lot of tears from all of us at times. It's a very tough condition and before my daughter started school there is no way my wife could have worked so we also lost one income.

Q6. Yes they should have.

Q7. Our daughter is behind on pretty much all her lessons. She struggles to focus for any length of time and looses knowledge quickly.
She struggles a lot with her tummy and at the age of 6 is already embarrassed by her toilet trips which i hate.
Emotionally i massively worry about the fact she basically has to force down supplement everyday of her life which sometimes makes her sick but she still has to drink it.

Q8. Our daughter is a very brave little girl and we try and make her life as happy as possible but ultimately her life is massively effected in a negative way due to this awful condition.

Q9. I believe this drug should be available freely to anyone who needs it.

Q10. RIDICULOUS there is scientific proof that high levels are dangerous for the foetus, so obviously i believe NICE are wrong.

Q11. As above.

Q12. How can you place a cost on this !

Q13. To sum up i feel we are way behind the rest of the world on this condition.
We need to give anyone with PKU at least the chance to respond to a life changing treatment but this trialing needs to be correctly dosed eg 20mg not 10mg. Then if a successful trial the person irrespective of age or sex should receive the correct dose age for life.

Respondent 19

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I welcome making Kuvan available to children under the age of 18 but the PKU diet is a diet for life. You can't just start it at 18yrs old. Your life would be miserable. I have a 15yr old son with PKU, I couldn't get him on KUVAN with the promise of a near normal diet only to take that away from him in 2 to 3 yrs. He's spent all his life learning to manage his diet and for the sake of 2 -3 yrs of normality he could mess up the rest of his life after he turned 18 yrs if he couldn't get back on the diet. A life time of high anxiety, depression, tiredness for the sake of a couple of years of eating properly. This decision makes no sense.

Q3. I do not agree with NICE's view;NICE's statements are contradictory;It's not just permanent brain damage it's a whole mental health issue.

Q4. I believe there is proof that the brain continues to develop well into your twenties. It's not just about permanent brain damage though, its about living with high phenylalanine levels and the depression and anxiety that it causes. Our own son with PKU , although under 18, suffers from severe anxiety and has missed nearly all his high school years due to it. He has recently started taking medication for this and has been able to attend a small private school but still can't manage to eat with the other children. I can't see how this anxiety would stop at 18yrs?

Q5. Managing the diet is extremely difficult. As parents of a child with PKU, we have found the diet extremely restrictive. We can't just go out to dinner at a local restaurant or pub. When we go on holiday most of our luggage allowance is used up taking low protein food with us. There is no spontaneity, we can't just head off out for the day and grab a bite to eat, we have to plan everything around food. As mentioned, our son refuses to stay at school to eat his lunch, one of us has to meet him for lunch everyday. If he could eat similar foods to the other kids he would eat at school and allow both of us to work. I remember when he was younger and we where at the bakers looking at all the bread and cakes and gingerbread men etc and he kept asking if he could eat this or that as he pointed to different things, I just had to say you can't eat anything in this shop.

Q6. PKU has a huge impact on our family. My wife doesn't work because she has to look after our PKU son. Preparing food, meeting him for lunch uses up a huge amount of her time. If he had a more normal diet, I doubt he would be costing the NHS money on anxiety tablets, specialist foods, counselling etc. we wouldn't constantly be trying to claim Disability Living Allowance. I expect having access to Kuvan would save the state money. My non-PKU daughters have had to suffer because as a family we just can't do many of the things normal families do. Just a simple ice cream on a day out to the beach would be wonderful.

Q7. I definitely agree that PKU causes anxiety , digestive problems and low moods as well as tiredness. Our son dropped out of main stream school in year 5, the anxiety got so bad we could no longer even drag down to the school. We've spent long periods not being able to go out as our son has been anxious about be separated from his mother as he is reliant on her for all his food. The tiredness and anxiety restricts him from joining in sports with other children and leads to obesity. It doesn't help that most of the foods available for him to eat are either sugar or fat based.

Q8. In addition to our regular quarterly sessions with the local paediatrician and dietrician our son is also regulating seeing a child psychiatrist under the care of the local children mental health team. In the past he has regularly been referred to councillors, phycologists and even a hypnotist. He's had various stomach scans due to digestive pains. Our local school put a huge amount of resource into various plans to try and get him into school and eventually had to have him home schooled after successfully gaining an EHCP for him. We have had to now cover the costs of a small private school just to try and get him interacting with other children.

Q9. I don't believe they have considered how PKU effects different groups. I don't know how anyone with learning disabilities or cognitive impairment could manage this diet. If you can't speak English it would be impossible to follow diet, things as simple as reading the ingredients would be difficult. If we were on a low income our son wouldn't be at school. A women wanting to conceive would be very scared attempting to strictly control her phenylalanine level. If you are ill and can't stomach any food then your levels can rise dangerously through no fault of your own. Kuvan could help in so many ways.

Q10. Surely pregnant women have enough worry about without the added stress of what high protein levels might be doing to their unborn child. Every women has the right to conceive and that should be made as stress free as possible.
Research in the USA concludes when a pregnant woman’s phenylalanine levels get too high, they can cause serious problems in her baby, including:
Intellectual disabilities
Microcephaly.
Heart defects
Low birthweight

Q11. Anything that avoids any problems to an unborn baby must be a good thing.

Q12. As mentioned, research shows that pregnant women with a raised Phe levels can lead to intellectual disabilities. The current recommendations suggest you would need to keep your levels spot on 3 months before falling pregnant. Falling pregnant is not always easy so a women with PKU who wants to fall pregnant could be having to manage that strict diet for years with the constant worry of her levels rising.

Q13. I welcome the fact that NICE are considering making KUVAN available to under 18 yrs but as this is a diet for life how could the treatment not be for life. Its ageist, what other condition would treatment stop at the age of 18? How can NICE expect under 18yrs to enjoy the life changing benefits of KUVAN only to have them taking away at the age of 18. They wouldn't be equipped to deal with such a drastic change of diet. This drug could improve the quality of life immeasurably for a small group of people, who, through no fault of their own, cannot enjoy life to the full because they can't eat anything. I cannot put a figure on the cost of KUVAN as apposed to not having KUVAN but I know our own son must have cost the state and ourselves tens of thousands each year - i can't see these costs going away when he reaches 18 yr. Surely KUVAN would be the cheaper option as well as the humane option.

Respondent 20

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I’d be doing a terrible disservice to my currently 15 month old baby boy if I was to allow him to take Kuvan and live an easier life in relation to food choices but then be completely unprepared to live his daily life and make food choices from 18 years old onwards. I am honestly shocked and appalled at this decision and hope everyone with PKU will be able to access Kuvan regardless of their age.
There’s a know saying - fail to prepare is to prepare to fail. I definitely want and need to prepare my little boy to understand how to count different foods (milks, sauces, dry foods etc that are often so confusing), where to shop for low protein foods, how to order foods on prescription and how to cook with them. He needs to have these knowledge and experience in order to survive and thrive in the real world on his own when he’s at university or a grown man with a job and his own family. Otherwise we’ll be risking him getting brain damage, mood swings, memory loss and other terrible effects that will prevent him from leading a great quality life.

Q3. NICE's statements are contradictory

Q4. N/A. Our boy is 15 months old so we don’t have this experience

Q5. A less strict diet would be very welcome. Currently as a carer I spent enormous amount of time planning my boy’s meals, ordering foods on prescription, reading forums on what other PKU parents cook or buy for their children, liaising with the nursery and its catering company on how to administer my boy’s medicine, how and what amount exchanges to give, what free foods should be prepared for him. Also extra time spent on cooking foods separately for my PKU baby and for the rest of the family, baking treats for children’s birthday parties he’s invited to where he cannot ear ordinary food etc.

Q6. Yes this should’ve been taken into consideration as planning and organising takes up so much time for the parents, never mind the constant worrying.

Q7. Yes I agree that children with PKU (but also everyone with PKU) need a treatment to reduce PKU symptoms. Thankfully we’ve been able to manage the phe levels fairly well with the help and guidance of our dietitian, and the use of SOS 15 medicine. However it has been difficult to keep phe levels within the desired range when our little boy was teething or caught a cold or virus and was poorly for some time.

Q8. N/A as our boy is 15 months old and has been keeping phe levels within desired range for most of the time

Q9. NICE is putting money above the welfare of the people which is unacceptable and frankly infuriating. It is discriminatory to offer treatment to people under 18 but not anyone over 18.
Kuvan is available in so many countries worldwide (even small European countries like Lithuania) that for it not to be available in the UK is very disappointing.

Q10. Everyone with PKU should get the treatment. And the people with PKU should then work closely with their respective dieticians to manage the risks.

Q11. N/A

Q12. N/A

Q13. N/A

Respondent 21

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I believe that if kuvan is going to be introduced for children it can not be taken away at 18 it must be a life time commitment to the treatment!

Q3. I do not agree with NICE's view

Q4. It’s not just the brain damage it’s the mental health effects, brain fog and personal struggles that a person had on a daily basis

Q5. Yes I think the use of kuvan would be great and allow my child to have a higher protein intake

Q6. Yes pku has a massive inpack on all close and extended family members and friends! My child often misses out on events and does not stay over in anyone else’s house and they are all to nervous on what she eats and measuring her food! It’s a massive impact and effects the mental health of family members! I had a total mental breakdown when my baby was born and lost the first year of her life due to pku!!!!

Q7. The temper tantrum’s my daughter has when bloods are high are exhausting for us as a family! She also does not sleep this impacts on my family and my work

Q8. There is extra costs for everything. Bread makers, waffle makers, even the cost of foods that have low protein or our vegan! I would say my shopping bill is an extra 100 a week to feed my daughter due to pku

Q9. All adults and children must be offered this treatment it’s against your human rights to offer to one group and not the other everyone is equal!

Q10. This is a disgrace been pregnant on top of pku would be very difficult expectant mothers need the help and support! Mental health issues will be caused if this does not happen

Q11. All adults must be given kuvan especially woman of child bearing age to reduce the risk of damages to a unborn baby! Again the unborn baby and the mother have the same rights!

Q12. Costs of mental health damage to mother can not be costed

Q13. All children and adults should be given the opportunity to see if kuvan will work for them! You can not provide a drug to help and support children until 18 and then take that away the mental health damage and suicide rate will go threw the roof! Equal rights and it’s everyone’s human right to be treated equally!!!!

Respondent 22

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Pku is a life long condition it does not stop at 18 years old.

Q3. I do not agree with NICE's view

Q4. No

Q5. Would definitely welcome the treatment for my daughter, would love her to have a normal life like her friends and family as much as possible without the stress and burden of pku

Q6. Yes pku is also a stress and burden on parents and carers

Q7. Yes definitely

Q8. *[no response given to this question]*

Q9. No it is not fair to treat people differently because of their situation

Q10. I think woman with pku should be allowed Kuvan

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 23

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. My daughter is 17, 18 in January 22. Her diet is even harder to manage now as a young adult than it ever was as a baby / young child. There are very few options regarding food when out socializing, therefore a simple shopping trip can result in no food been consumed. Her levels fluctuate dramatically despite regularly taking supplements. Her concentration is effected when levels are high, also is her ability to process and retain information which has meant she has struggled in school/college to be like her peers. The sheer idea that this issue goes away as soon as a person reaches 18 is ridicules and to argue the case that an adult weights more therefore will cost more is just an insult! The financial cost of PKU on a family already exceeds that of a "normal" family food budget and the fact that you are denied any financial help only adds to this. If

Kuvan for child and adult will stop the financial and mental burden then for the society it is worth the cost. I do not see other conditions having medication stopped at 18 such as diabetes, epilepsy the list could go on.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. Adult concentration levels are effected by high Phe levels is this not related to the brain???

Q5. I absolutely agree that Kuvan and the chance of having a more normal diet will greatly reduce stress within the family. The strict diet completely runs the life of the family. There can not be a family outing or social event that does not need planning strictly before hand. The financial cost is great as you have to buy more specialized foods and you are unable to get any financial help from the government!!! this condition ultimately led to the breakdown of our family unit as the constant confliction broke the family!

Q6. Yes - Raising a child / young adult with PKU puta a massive strain on family and also the relationship between child and parent. The amount of arguments and tears this condition has caused. My daughter has also had to go for counselling due to PKU and its impacts.

Q7. My daughter has suffered anxiety due to PKU and has needed counselling in the past. Kuvan would give peace of mind but i worry my daughter will miss out as she is 17, 18 in January 2022

Q8. Quality of life is massively effected due to the social isolation they experience. As a young child my daughter was excluded from friends parties and gatherings as parents were scared of her condition. Also the ability to enjoy life without having to constantly think what am i going to eat!!!

Q9. This is a completely money focused decision all patient with PKU should have a chance of being able to enjoy food and enjoy not having limits on their life's.

Q10. Kuvan should be given to PKU ladies wanting to try for a child are they not aware that bad control can lead to a severely mentally handicaped child which would certainly put a greater financial burden on the country ! All female should be given Kuvan incase of unplanned pregnancy.

Q11. All female should be given Kuvan incase of unplanned pregnancy. A handicapped child would put a much greater financial burden on the country than a small population of female PKU patients surely!

Q12. See comment above

Q13. Surely to not include all Pku patients is discrimination! i don't think diabetics are told they can't have treatment when they reach adulthood. This is a long term condition with life changing effects on the patient but also on the family. This condition has effected my family massively and resulted in the break up of my relationship with my daughters father has he could not cope with the demands of the condition. Please give my daughter at least a chance of a more fulfilled life without limitations.

If a child is on Kuvan would this be stopped at 18 or would it be stopped? Surely this can not be right again i go back to a diabetic patient or anyone with a long term condition.

Respondent 24

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. It seems unreasonable to accustom somebody both physically and mentally throughout their formative years to a major part of their life only to require that aspect of their lives to be fundamentally changed upon turning 18. Such a change could be mind shattering unless private resources exist which could take the place of NHS provision.

Q3. I do not have the knowledge to comment as to the risk of physical brain damage but am in little doubt as to the probability of profound psychological damage if the treatment is suddenly denied

Q4. No personal experience.

Q5. I agree strongly. The fear of brain damage to one's loved one is a huge cause of stress over and above that caused by the mechanical aspects of meeting special dietary requirements both within the home and elsewhere.

Q6. Without doubt. See previous answer.

Q7. Unable to comment. these are early days yet for our sufferer although there are indications that such problems may arise.

Q8. There is no doubt that there are additional costs and constraints.

Q9. II do not have information to form an opinion.

Q10. Given that child bearing is a fundamental right and function it is important that adequare research should take place into this matter.

Q11. *[no response given to this question]*

Q12. To the extent that children of PKU sufferers are at risk this is a significant additional result of the condition and should therefore be taken into account.

Q13. *[no response given to this question]*

Respondent 25

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Great news allowing under 18s to finally have the drug which will change their lives, but taking it away when they are 18 is disgraceful and would lead to teenage mental health problems and cause depression as they wouldn't be able to continue their life they had up to 18 on the drugs

Q3. I do not agree with NICE's view

Q4. Do your research adults have shadowing I'd off diet on brain which causes MS symptoms along with a number of other health implications

Q5. Yes

Q6. Yes

Q7. Yes 100% agree

Q8. Yes - costs are involved with all of the help and extra support child receive at school and other areas

Q9. No

Q10. *[no response given to this question]*

Q11. This is one of the reasons why it should not be stopped at 18

Q12. No

Q13. Extend this to all ages!

Respondent 26

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. With Kuvan, my daughter's diet would allow her approx double the amount of protein she is allowed today. Why would you let her increase her protein intake and then half it again at the age of 18 once she has gotten used to the increased amount. This seems a very cruel way to treat young adults who have this condition through no fault of their own.

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. A less strict protein-restricted diet would be welcomed in our house especially now my daughter is a teenager and I have less control over what she eats.

Q6. The impact on other family members should definitely have been taken into account. There is time, money & effort put into sourcing foods that your child can eat. Travelling to Tesco/ASDA supermarkets 40/50 miles away from home to see if they have the 1g protein frozen veggie burgers in stock as the substitutes in the local store won't do.

Q7. There needs to be a treatment that helps your child reduce all the symptoms of PKU and also give parents/carers peace of mind over the blood test results.

Q8. Maybe information should be routinely collected and then a more informed choice can be made? Seems that once you hit 18 you are on your own.

Q9. NICE is not treating people fairly. There are adults that get treatment for self inflicted illnesses (drugs/alcohol/obesity) yet someone born with a genetic condition that isn't life threatening are told sorry - you're condition is not cost effective ! Disgusting !

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 27

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Why til 18 let people pku carry on taking it

Q3. I agree with NICE's view that there is no risk of long term brain damage in people with PKU aged over 18

Q4. *[no response given to this question]*

Q5. Yes

Q6. Yes

Q7. I agree

Q8. No

Q9. Yes

Q10. No

Q11. No

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 28

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. It would be cruel to stop the treatment after when a child is 18yo by law. They would get used to the benefits of using Kuvan (being able to eat more protein from widely available food items, not being restricted by a low phe diet, being more in control of what they could eat, being more empowered in their adult life, avoiding the risk of getting all of the nasty side effects of phe level above the range - from a nervous system etc., being anxiety free and being and feeling safe and secure for the future - prospective mothers who have pku etc). PKU is a long life disase.

Q3. I do not agree with NICE's view;NICE's statements are contradictory;A well funtioning brain is needed for the life time of every person.

Q4. A well working brain is a must for all people for the life time. When a person has any health impairement or a life long disease of which brain function is badly affected, it is vital to equip the person with anything possible to avoid or to keep in control any existing brain disfunction or damage. Although it is said that brain develops until certain age (NICE contradicts themself on this), and that time is extremely important, it is known that brain activity can be badly disturbed by too low or too high levels of the substances (serotonine re depression etc and phe re pku in this situation). A well working brain needs a continuity of well balanced organic substances etc. for the rest of a person's life not just until they are 18yo by law.

Q5. I agree, therefore, Kuvan must be available to all people with pku.
PKU does not magicaly vanish after a person with pku turns 18yo by law.
You always must be ready and in control as much as possible to look after your child/childrrn with pku.

Q6. Yes, NICE should include the impact of pku on other family members when valuing treatments for pku. There are a huge responsibility of parents/carers etc'shoulders when in comes to managing a pku diet. All must be done acurately, counting out protein exchanges, providing food items that are low protein ones and included in a dialy menu. Apart from special dietary items on prescription that are very often prescribed incorrectly, not understood by gp's practices, phe free protein supplements are artificial anyway but are a crucial part of low phe diet.

Q7. Agree, and therefore Kuvan should be available to them all the time not only till they aren18yo by law. PKU is a life long condition.

Q8. The data is not collected as PKU is called a RARE genetic disorder and it looks as if the needs for this have been ignored or belittled.

Q9. NICE should look at a wider picture of this all. Kuvan could be treated as a prevention of future health problems in people with pku who find managing a low phe diet hard and therefore lower the associated costs in the future.
PKU is for life, it does not disapear when a person is 18yo by law.

Q10. NICE should recommend Kuvan to help women manage the risk of maternal pku. It is always said that prevention is better that treatment.

Q11. PKU is a LIFE LONG DISEASE and it should be looked at it this way.

Q12. I would said that it is a bad practice of NICE to omit any reports and evidence that are already available and could help form a true picture of severity of pku.
NICE should include the reports.

Q13. PKU is a disease that is in a person for life and do not stop existing when they are 18yo by law. It would be cruel and non human to take away a medicine that helps them with managing treatment and prevention of pku bad and irreversible symptoms.
People are born with pku, they have no choice whether to have it or not. PKU is not a disease that happen to people due to their wrong life/diet etc choices. It is a disease that stays with them untill the end of their lives. There are many money spent on treatment and/or keeping side effects of other diseases on easy, that occur because people decided to do yourself wrong (smoking, bad diet, drug and alcohol misuse etc) and yet it is not a problem. But funding the medicine, Kuvan, that is widely available abroad is still a huge issue in the rich country which is the UK.
IT MUST CHANGE.
THANK YOU.

Respondent 29

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I think that this would be dangerous and also negligent to the duty of care for the child. Kuvan has the potential to allow a child to be able to commence and normal diet without restrictions and to discontinue it at 18, would be detriment to the child's ability to plan his or hers diet in future and to manage it

Q3. NICE's statements are contradictory

Q4. i have no experiance from a family, but have come into contact with adults with severe learning difficulties due to brain damage from PKU

Q5. agree, this would allow family to be more flexible and welcoming in their dietary intake and to experience new and meaningful experiances. alos the worry fro brain damage is lessened and will decrease the stress with it. Mental health of carers will improve

Q6. yes, pku has been known to increase the financial cost to the family units. Specialist food do come at a higher cost, and vegan variants that are suitable are high in cost.

Q7. agree

Q8. *[no response given to this question]*

Q9. *[no response given to this question]*

Q10. I think nice should recommend for women, there is evidence from USA,Europe that shows the benefits. Nice is excluding these evidences due to financial costs

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. NICE has a duty of care towards those who have uncontrolled or needing a viable treatment option for PKU, this should overrule cost, for the statements for no evidence exists, nice needs to look at the licensing in mainland Europe and North America where Kuvan is prescribed

Respondent 30

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. My twins are 3 both have PKU. They are to young to understand PKU & the very extreme strict diet they have to adhere to every single day. If they started to take Kuvan now & they responded and then be told on their 18th birthday that the drug that has completely changed their life is being taken away how ever do you expect them to go back on the very extreme strict diet. They would have no memory of our lives now & how VERY difficult it is. They wouldnt no how to live on the extreme strict diet. Turning 18 is a huge milestone , they could be leaving home, starting uni etc etc. Then they are told thats it your life is going to change for the worst you wont beable to eat anything you are eating now. You will only be allowed 9gm of protein each day, you will have to weigh every morsel of food, you will have to check every label on foods, you have check all ingredients of everything you eat and drink. You will have to take discusting supplements 3 times per day. You wont ever get a day off from this its every day forever. You could suffer seizures, learning difficulties, irreversable brain damage.
If you are a parent please put yourself in my shoes. Can you imagine telling your 18 year old child on their 18 birthday?
Its not ethical. I think you really need to understand PKU before you 100% decide that this is the right decision. This will cause alot of mental health issues to many people. I invite you to see a day on my life, then im sure yoy would understand the impact this will have to my 2 beautiful girls. How can you give a life changing drug to somebody and then take it away when they are 18? Its shocking !

Q3. I do not agree with NICE's view

Q4. *[no response given to this question]*

Q5. Yes. I had to give up my fulltime job and be my twins carer. This is a 24/7 job. I have had counselling because PKU life is so hard and so stressful every single day. There is no day off. Not Christmas, not birthdays its 24/7. You have to constantly watch your child incase they eat or drink something that could cause brain damage. The pressure is immense. It has caused strains on my relationships with my husband and my family. As the condition is so rare nobody has heard of it and its very difficult to explain. Even after you have explained it some people think its a food allergy.
Its very draining having to explain to everyone what the condition is. I am scared when my girls go to nursery that they will eat of drink something they are not allowed. I am scared they will get ill as this will cause the PHE levels to be out of range. I am scared to let my girls go to family incase they eat or drink something they are not allowed. I take food and supplement in the car eveytime i go out incase we get stuck anywhere, you have to be prepared for every situation as i cannit just pop in the shop if the girls are hungry i have to have food prepared. I take scales everywherei go to weigh food. This is so much more than just a diet. This is the most stressful experience i have ever had. I am.completely exhausted.

Q6. Yes NICE should have taken this into account . PKU effects every family member. Everyone in the family needs to be fully aware of the condition and how its managed

Q7. *[no response given to this question]*

Q8. There is no quality of life living with PKU. My girls were misunderstood at nursery. The keyworker automatically thought my girls had learning difficulties because of PKU and wanted to refer them to early years intervention! Im dreading them starting school and being misunderstood again. They deserve to live the best life i can possibly give them. PKU does not stop at 18. Infact PKU life at 18 will get MUCH harder.

Q9. *[no response given to this question]*

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. The amount of money spent on prescription foods for people with PKU is outrageous. If everybody with PKU was given PKU for LIFE and they responded the amount of money that would saved is imaginable.

Respondent 31

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. This medication should be available throughout their lives. It would be cruel to stop the medication once they are used to eating foods with a higher protein content just because they have turned 18. Especially too as with most youngesters starting university or college at this age, the peer pressure to eat the wrong foods could cause lots to damage to their brains, mental health and well-being.

Q3. I do not agree with NICE's view

Q4. *[no response given to this question]*

Q5. Very much so. It has been extremely difficult to get both medical and lay people to understand my son dietary needs. I'm often made to feel as if I'm asking too much or if my sons needs can be met in the gluten free isle of a supermarket which is ludicrous.

Q6. Absolutely they should have. Managing my sons diet is very time consuming both whilst shopping and doing meal prep. If he's fed something by a family member I have to change everything to compensate. Due to his dietary needs he can't spend much time away from me as many other family members and friends do not understand his diet or restrictions and this leads to much anxiety and stress when he's away from me.

Q7. I do agree. When my sons levels are high, he gets agitated very easily. He is prone to emotional outbursts that are not normal to his character and his dietary restrictions depress him, especially when he watches his siblings and friends eating things he can't have.

Q8. I think that is wrong, they only need to talk to the parents of children with PKU to know that there is definitely an effect to those people who deal with or suffer with PKU. I understand that they may have trouble quantifying the costs but it doesn't mean that there aren't any.
Parents trips to hospital appointments
Regular difficulties in shopping
Inability to take your family out to eat
Regular trips/consultations with Dietians
Difficulty in allowing others to feed your child, especially schools/childcare meaning that the parent has to work part time hours to provide the care their child needs

Q9. No not at all. The mental health services, dietary requirements with prescription foods and the regular hospital appointments need to be considered as well as the long term effects of brain damage and the social care these adults may require of off diet long term. I feel this is a very shortsighted view. I am guessing that none of those that have made these recommendations have either suffered with or care for a child/adult with PKU and I believe strongly that they wouldn't have come to this conclusion if they had.

Q10. That they should relook at this. Data should be looked at from countries such as Russia where pku diagnosis isn't as readily available.

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 32

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I think kuvan should be available for all ages of children and adults with pku. To suddenly stop at age 18 when you could be still in education ie university or just starting a working life would have a huge detrimental affect on someone's life. To open out extra choices for someone and then take it away is extremely detrimental to mental health and will cause many people extreme anguish.

Q3. NICE's statements are contradictory

Q4. I have no knowledge of long term brain damage but my mother had Alzheimer's for many years, surely it is better to do all you can to prevent brain damage than to wilfully let it happen.

Q5. I do agree, both parents usually need to work these days and to have additional stress of managing two children's (some have more children) dietary requirements as well as holding down full time work is not easy. Every little extra allowance of protein food is helpful when trying to organise a strict diet for children and adults with pku.

Q6. Everything needs to be taken into account when valuing treatments, nice only look at the short term but in the long the effects of such a restricted diet is far reaching.

Q7. At the moment my grandchildren are still very young and as yet they don't have these problems but I can imagine children who are teenagers could be highly affected by such a restrictive diet.

Q8. At the moment my grandchildren are very young and it is dealt with so well by my daughter snd her husband that I'm not sure it How it impacts their life other than restricting their choices.

Q9. *[no response given to this question]*

Q10. *[no response given to this question]*

Q11. Yes kuvan should be available to woman of child bearing age.

Q12. These long term effects should always be taken into consideration as it always will cost more to address in the long term.

Q13. *[no response given to this question]*

Respondent 33

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. PKU is a life long disease. It does not finish when a person reaches 18yo by law.
It would be cruel to refrain from providing Kuvan for people previously on it only because they are adults. The children/teenagers with pku on Kuvan would be able to be on less restricted diet, get used to it and then suddenly would have to stop using it and return to a full low phe diet, change their way of managing pku and living - Kuvan to be available for all.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. A brain function depends on many factors, including the right level of particular substances, in this situation, phe and tirosine levels. Although it is said that brain development is the most intense during childhood, it does not mean that after this period phe levels that are out of the range does not badly affect the brain.

Q5. I agree and therefore Kuvan availability should be continued after the children and teenagers with pku are 18yo by law.
Managing pku is a life long journey, it affects people diagnosed with pku and also other people in the family.

Q6. Yes, NICE should include the impact of pku on other family members.

Q7. PKU continues for life, it does not end when a diagnosed person is 18yo by law. Managing phe levels matters throughout a life time.

Q8. PKU as a RARE genetic disease is being not much aknowledged and needs of the people diagnosed with pku and people involved in their care are ignored.

Q9. NICE recommendations do not treat all groups of peoole with pku fairly. Kuvan should be available to all people with pku as it is a life long disease. Some diagnosed people who are badly affected by pku are not able to manage thier low phe diet. Imagine a child with pku with impairement in their learning or a woman with pku who would like to become pregnant but does not do it due to fear of real risks to a baby to get a maternal pku.

Q10. Kuvan should be available to all women with pku. There are real risks for babies of mothers with pku, resulting from a maternal pku.

Q11. Kuvan must be available to all women with pku. It helps managing phe levels, which are crucial (within the range) for growing babies in their mothers wombs.

Q12. This should be included.

Q13. PKU is a life long disease and Kuvan must be available to all people with pku.
NICE should consider any future cost related matters - not funding Kuvan for everyone with PKU could generate further costs in the future.
Kuvan for all with pku.
Thank you

Respondent 34

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. It is stupid to choose a cheaper medication that provided prescription food at a cost of over £1000 a month.

Q3. I do not agree with NICE's view

Q4. Many off diet PKUers I have met at annual PKU conferences display significant brain damage and lack of mental agility

Q5. Yes it would significant help reduce the burden of care and the risks of keeping people on a very limited strict diet

Q6. Kuvan would be cheaper for our child that the huge amount spent on his prescription food. and we spend an equally huge amount on veg and salads as he cant each much else. kuvan would enable him to eat a more normal diet so we don't have to shop and cook two different meals every meal times

Q7. Yes he also has ADHD and there are links between the two + normal teenage behaviours on top trying to fit in where they cant

Q8. This should not be means tested. Parents who work have evcen less time to do all the extra cooking etc and ordering prescription and preparing 2 sets of meals 3 times a day

Q9. Complete rubbish. the medication creates greater dietary options the majority of which are cheaper and with a range of beneficial outcomes

Q10. Not sure

Q11. Not sure

Q12. This is a key fact that needs to be factored in. PKU in adults or kids adds another person into the mental health waiting lists, less likely to get a job and create GDP for the UK

Q13. The NICE report is shallow. benefit versus costs analysis has not taken into the real case examples. This could be added by asking NSPKU families for volunteers to create a range of evidence that means something not just random stats taken out of whole through-life context.

Respondent 35

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. As the child gets older the strict diet gets harder, adolescents and adults would benefit from Kuvan because it would help to ease some of the difficulties of having PKU especially at college or university

Q3. I do not agree with NICE's view

Q4. No

Q5. Agree with all of the above but this doesn’t stop when the Child gets to 18.

Q6. Yes they should take all the above into account

Q7. I agree, my grandson, aged 16 has had all of the above symptoms

Q8. Schools and college catering departments should be more informed about the requirements of someone with PKU

Q9. Everyone with PKU should have Kuvan and the people as above should have easy access to get help with the management of the diet.

Q10. *[no response given to this question]*

Q11. No

Q12. No

Q13. *[no response given to this question]*

Respondent 36

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. My grandson ,aged 19,has just started university and away from home for the first time.His mother has been wonderful in trying prepare him to take care of himself but to have Kuvan available to him now would means so much.I cannot imagine what it would be like if this treatment had been available to him until now and then withdrawn when he probably needs it most.

Q3. I do not agree with NICE's view

Q4. No.I do,however,know how hard the last 18 years have been for our little lad who never openly complains but must have found it hard at times 'being different'.How could a child adapt at the most difficult time in their lives,to date.?

Q5. it is very hard for parents and sometimes for siblings not similarly affected.We do not live close enough to help much but Grannie has always tried to prepare some treats within the guidelines.Our grandson has been confirmed as suitable to receive Kuvan and for them to eat some part of a meal as a family would be wonderful.

Q6. see above

Q7. we have seen some dips in mood which is hardly surprising.our grandson is probably underweight for his age which is not surprising in view of his limited diet.Robust games are difficult but he always tried to join in when he was younger.

Q8. there is some sacrifice which the family are happy to live with.Money is not an issue but there are extra costs to consider.

Q9. I can imagine that this illness can be very difficult to manage in some family situations especially if there are multiple cases.I am aware of one family with three 'sufferers'

Q10. no knowledge.

Q11. No experience

Q12. As above

Q13. it would be wonderful for these dedicated parents to know that their offspring could lead a more independent life,and for the rest of their lives.The cost of any long term treatment is appreciated and there are many demands on the cash strapped NHS Tthe end of 'copyright' for the medicine will reduce the cost possibly quite significantly and this must be the time to help everyone.I have been on daily aspirin for many years,who would have thought this would be viable when it was discovered!!Time to give these families some hope.

Respondent 37

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I would class this as cruel to give someone the chance of a much better quality of life and then snatch that away.

Q3. NICE's statements are contradictory

Q4. NICE obviously totally contradict themselves.in their statements. I only know what i have read written by PKU sufferers all often complain of various mental issues.

Q5. This condition brings stress to everyone in our household. Especially my wife he deals with most of my daughters dietary requirements. This along side virtually false feeding a child a foul tasting supplement 3 times a day is very hard.
There’s no way my wife could of worked before our daughter was school age, so we lost an income.

Q6. Yes they should have.

Q7. Yes i agree.
My daughter suffers a lot with focus, upset tummy's etc etc

Q8. It effects anyone with PKU life massively. You need to forward plan all food, drink and supplements. Often need to be near a toilet and many other things a non PKU person doesn't need to think of.

Q9. I dont think anything NICE have done is fair. I cant comment on special needs groups etc but i do feel all groups should have equal rites to the drug.

Q10. It's been scientifically proven that bad levels effect the foetus so this is a ridiculous comment !

Q11. No

Q12. No

Q13. Simply anyone with this very difficult condition needs to be trialed for a potentially life changing treatment and treated at the correct dosage. I would personally give anything to improve my little girls life.

Respondent 38

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. We are concerned about the mental health implications of an 18 year old having to significantly adjust their lifestyle due to having to adopt a severely restrictive PKU diet having not had the experience of living with the diet or knowledge to do it independently. Mental health issues are also of concern for a young adult having to suddenly and dramatically adjust their lifestyle socially (this is a major implication of PKU on young children eg the challenges of children living a normal life with friends when eating out is so restrictive). Further, at 18, higher education and work are a significant part of a young adults life and to suddenly have to deal with the highly restrictive PKU diet whilst having a lack of experience to do so, could have severe implications for their mental health.

Q3. NICE's statements are contradictory

Q4. The NICE statement is contradictory given it suggests brain damage is possible up to 25 whilst also stating that there is no risk in adults. It is a concern that the years between 18 and 25 seem not to matter in terms of the risk of brain damage.

Q5. Living with a child with PKU is exactly as prescribed above and does put significant strain on and impacts careers/parents own mental health. To be faced with the possibility of a child growing up with Kuvan and a less restrictive diet and then having to adjust to a highly restrictive diet at 18 when Kuvan is withdrawn, would mean that parents/careers would have to face many more years dealing with these challenges given their child would be poorly equipped to cope on their own (given the last of experience) and the broader impact on their own mental health.

Q6. *[no response given to this question]*

Q7. Our concern here is that NICE have recognised the impact of the PKU systems and stated the need for a treatment, yet are proposing to remove this treatment at 18, a time when young adults are at their most stressful time (as they start their adult lives, face higher education, living away from home, start working possibly for the first time and face having to become more independent). This could lead to significant mental health and physical health issues when coupled with the PKU symptoms and likelihood that given the lack of prior experience managing the restructure diet, could exacerbate.

Q8. *[no response given to this question]*

Q9. *[no response given to this question]*

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 39

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. PKU is a life long condition that needs to be adhered to throughout adulthood. To suddenly stop at the age of 18 will be detrimental to health and mental health.

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. The closely monitored diet is an ongoing battle that some government funded schools are not able to monitor. Therefore private education is the best way to ensure the diet is adhered too.
The stress and pressures on home relationships from keeping up with the supplements causes an immense amount of stress. Often singling out children leading to them asking questions about why they are different. The digestive challenges they face, mental challenges, physical challenges, they are all very difficult to manage.

Q6. The way NICE have valued PKU is concerning. The emotional and physical value on the PKU sufferer and support network has not been considered

Q7. Yes I agree however the dose must be increased

Q8. As above the extra educational and social costs have not been considered here. As PKU is pretty much unheard of, no where caters for this which in turn leads to more challenges around socially enjoyment and interaction with others. For families with a low income, this must be almost impossible to manage.

Q9. NICE has not fairly considered how this affects the wide range of families in the UK today. It has not considered income, social, emotional, physical outcomes.

Q10. NICE have not considered the detrimental affects this will have on the unborn baby. Brain damage leading to further medical issues etc will all increase if Kuvan is not offered to adults during and pre pregnancy. I understood this to currently be available whilst pregnant and therefor is makes no sense why this is being removed. The cost to the NHS for managing a more medically comprised/ disabled child must be much more than the cost of giving Kuvan pre and during Kuvan.

Q11. As above

Q12. As above

Q13. The dose of Kuvan should be increased. A cap of 10mg is not high enough. Most people are know to respond between 10-20mg. If the dose is capped at 10. The response rate will again be halved.

Respondent 40

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. This proposal is setting young adults (and older) with PKU up to fail. Without Kuvan, individuals can not eat an enormous amount of regular foods so this proposal is potentially allowing them to increase this amount significantly only to be taken away once 18. At 18 years old, many young people will leave home, go to uni or maybe choose to travel. How can these young people be expected to completely change their known diet and switch to an extremely strict low protein diet with support? Not only can my son not eat meat, (all varieties, including beef, lamb, pork, ham, bacon, chicken, turkey, duck and
game), fish, egg, cheese, nuts, seeds, soya etc he can not even eat regular bread or pasta!! Everything would change! Even the amount of peas on his plate!

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. As a community, we are aware of the effects PKU has on brain development/damage. Adults have shared stories asking for help and advice for their mental and physical health throughout their lives. This does not stop at 18 years old or even 25. This is a life long condition with everyday, life long effects on health and quality of life.

Q5. Yes, absolutely. Caring for a child with PKU is a massive strain and a huge responsibly. Every single piece of food has to be thought carefully about. The knowledge that if you as a parent give your child the wrong foods could lead to permanent brain damage fills you with anxiety and stress, every day! You need to plan your daily meals right down to how much broccoli you give at tea time or even if you can give him any depending on what he has eaten through the day. My son has asked me for more vegetables many times and I have had to say no. This is unfair, heartbreaking and cruel. This is a 3 years old. Imagine this, he gets on Kuvan, he's tolerance improves, then at 18 years old, it's taken away and he goes back to what he can now eat as a 3 year old.

I extended my maternity leave to stay at home as the thought of handing over responsibly for food to someone else was too much!

Just last week, I was taken into hospital. My husband had to leave me to sort out food and supplements for our son as he had to stay with family. Even going to Grandma's for a night causes stress and worry when this should be the opposite.

Q6. Yes. Having a family member with PKU effects everyone in the family. Personally, we have all changed our diet, however we still have to eat different foods to ensure we get enough protein. Again, is comes down to planning everything. We can not be spontaneous as a family and decide last minute we want a chippy tea. We can not just pop into a restaurant on the way home from a day out. If travelling, we need to contact the airline and explain in detail the condition as we need extra luggage for supplements and food. He can not eat airplane food so we are stopped at security about why we are carrying food with us so we need to explain the whole thing again! And all the while, there is a little boy stood there often feeling victimised/sad/upset/embarrassed/angry. Regardless of COVID, we have done nowhere near the amount of travelling we had planned to do with our family due to pressures of having the PKU diet to think about. Why should our son or the rest of his family miss out on these life experiences??

Q7. Yes, I agree. As our son in young he is unable to describe or explain his feelings. There have been times when we predicted high levels due to him being more unsettled and out of sorts. Often, we have been right and seen higher levels at the next blood test.

Q8. We do our best every day to make sure the quality of our sons life is not affected however, as previously explained, this is impossible. Thankfully, we have not had to access any additional support from early help or social services. I do however see how these services could be vital for some families.

Q9. These comments are unfair. EVERYONE will PKU needs support. All the groups included above are valid. If anything, this condition gets harder to keep under control as you get older and are left to try to control phe levels more independently.

Q10. The committee need to become aware of evidence before making a decision. Controlling phe levels are obviously much more difficult during pregnancy which will evidently have a knock on effect to the health and well being of the carrying mother.

Q11. This is vital!

Q12. Everything needs to be considered. The impact of having PKU has a rippling effect.

Q13. A life long treatment is required for a life long condition. PKU effects a person physically, mentally, socially and emotionally. This is not just a 'diet'. It is a lifestyle which has been dumped on a person with no choice in the matter. There are many many self inflicted conditions treated for life. Why are people with PKU being treated differently?

Respondent 41

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. The current diet which must be followed by my child with PKU is extremely restrictive and strict. Everything she eats must be carefully calculated and weighed. The notion that a child was on Kuvan (which allows a much more relaxed diet) and then suddenly at the age of 18 had to learn to restrict themselves to an extremely low protein diet is completely absurd. Most 18 year olds are struggling with new found independence and finding their way in the world. To expect them to suddenly fundamentally change their entire diet on their 18th birthday is fanciful at best.

Q3. NICE's statements are contradictory

Q4. I am a Doctor and a mum of a 2 year old with PKU. I have experience of caring for adults with varying degrees of brain damage and mental impairment. A human brain does not suddenly stop developing at the age of 18 - infact it continues to develop into their mid-20s. Restricting the licence of Kuvan to under 18s only would significanlty increase the risk of long term brain damage and impairment in young adults between 18-25 years who will struggle to control Phenylalanine levels tightly when suddenly having to adjust to a strict low protein diet.

Q5. I absolutely agree with the above. As a mum to a 2 year old with PKU I have had to cut my hours to part-time. I was diagnosed with post-partum anxiety and depression which was triggered by the daily anxiety of managing my daughters Phe blood levels. I was paranoid that if I made a mistake with calculations it would result in brain damage.
All nurseries in my local area where not able to provide food for my child so each day I have to prepare all her food for the day prior to nursery. Then, once she returns I must carefully weigh any remaining food and calculate her protein intake deficit. I then spend the evening trying to get my fussy toddler to eat the correct foods to hit her protein target for the day. Whie my daughter is only 2 she is already noticing that she is eating different foods at nursery to her peers. While I try and match the foods I make with what nursery provides sometimes this is just not possible. If she was on Kuvan and able to tolerate more protein it would take a huge pressure off of parents when trying to prepare meals.

Q6. NICE needs to realise the knock-on effect of their "economic decision". I know that if my child didn't have PKU I would likely be working full time rather than part time. I know that caring for a child with PKU will undoubtably get harder as they get older - and particularly in the teenage years where they will try and push boudaries.

Q7. I absolutely agree with the above. While my daughter is only 2 we have had ongoing issues with her digestive system and in particular chronic constipation which I fully attribute to her supplements that she must take due to her extremely protein restricted diet. I have a strong family history of anxiety and depression and am extremely worried about my daughters increased risk of developing mental health issues given her strong family history and her PKU.

Q8. In the first year of my daughters life I had to access maternal mental health services to help with post partum anxiety and depression which was triggered by the diagnosis of PKU in my daughter.

Q9. While I agree with NICE that there may be wide breadth of disadvantaged people that may struggle with following a PKU diet I think it short sighted and incorrect to say that they cannot recommend Kuvan in any group of adults. As with all new medications and technology there is a cost/benefit analysis. Surely Kuvan should be recommended in adults with the greatest risk of consequences of not achieving tightly controlled Phe levels. As an example - surely in pregnancy the consequences of poorly controlled Phe level would be devastating on a developing fetus. Furthermore, rather than recommending Kuvan in any sub group of adults surely Kuvan should considered in adults failing to achieve controlled Phe levels despite adequate/ maximal intervention i.e. metabolic dietician input/ nurse specialist input/ dietary monitoring.

Q10. I think that Kuvan should be recommended in maternal PKU and pregnancy. The degree of monitoring and extremely strict diet control required in pregnancy is huge. Add to this the nausea/ vomitting/ food cravings all experienced in pregnancy and this all adds up to an extremely testing time for PKU mothers. Any intervention which could make the pregnancy easy must surely be considered.

Q11. I think that Kuvan should be recommended in maternal PKU and pregnancy. The degree of monitoring and extremely strict diet control required in pregnancy is huge. Add to this the nausea/ vomitting/ food cravings all experienced in pregnancy and this all adds up to an extremely testing time for PKU mothers. Any intervention which could make the pregnancy easy must surely be considered.

Q12. Surely this is extremly short sighted. The cost of longterm care for a child born with significant and irreversible brain damage is not insignificant.

Q13. *[no response given to this question]*

Respondent 42

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I welcome making Kuvan available to children under the age of 18 but the PKU diet is a diet for life. You can't just start it at 18yrs old. Your life would be miserable. We have a 15yr old son with PKU, we cant get him on KUVAN with the promise of a near normal diet only to take that away from him in 2 to 3 yrs. He's spent all his life learning to manage his diet and for the sake of 2 -3 yrs of normality he could mess up the rest of his life after he turned 18 yrs if he couldn't get back on the diet. A life time of high anxiety, depression, tiredness for the sake of a couple of years of eating properly. This decision makes no sense.
I believe there is proof that the brain continues to develop well into your twenties. It's not just about permanent brain damage though, its about living with high phenylalanine levels and the depression and anxiety that it causes. Our own son with PKU , although under 18, suffers from

severe anxiety and has missed nearly all his high school years due to it. He has recently started taking medication for this and has been able to attend a small private school but still can't manage to eat with the other children. I can't see how this anxiety would stop at 18yrs?

Q3. I do not agree with NICE's view;NICE's statements are contradictory;Its not just about high risk of permanent brain damage its mental health as a whole

Q4. I believe there is proof that the brain continues to develop well into your twenties. It's not just about permanent brain damage though, its about living with high phenlylaline levels and the depression and anxiety that it causes. Our own son with PKU , although under 18, suffers from severe anxiety and has missed nearly all his high school years due to it. He has recently started taking medication for this and has been able to attend a small private school but still can't manage to eat with the other children. I can't see how this anxiety would stop at 18yrs?

Q5. Managing the diet is extremely difficult. As parents of a child with PKU, we have found the diet extremely restrictive. We can't just go out to dinner at a local restaurant or pub. When we go on holiday most of our luggage allowance is used up taking low protein food with us. There is no spontaneity, we can't just head off out for the day and grab a bite to eat, we have to plan everything around food. As mentioned, our son refuses to stay at school to eat his lunch, one of us has to meet him for lunch everyday. If he could eat similar foods to the other kids he would eat at school and allow both of us to work. I remember when he was younger and we where at the bakers looking at all the bread and cakes and gingerbread men etc and he kept asking if he could eat this or that as he pointed to different things, I just had to say you can't eat anything in this shop.

Q6. PKU has a huge impact on our family. My wife doesn't work because she has to look after our PKU son. Preparing food, meeting him for lunch uses up a huge amount of her time. If he had a more normal diet, I doubt he would be costing the NHS money on anxiety tablets, specialist foods, counselling etc. we wouldn't constantly be trying to claim Disability Living Allowance. I expect having access to Kuvan would save the state money. My non-PKU daughters have had to suffer because as a family we just can't do many of the things normal families do. Just a simple ice cream on a day out to the beach would be wonderful.

Q7. I definitely agree that PKU causes anxiety , digestive problems and low moods as well as tiredness. Our son dropped out of main stream school in year 5, the anxiety got so bad we could no longer even drag down to the school. We've spent long periods not being able to go out as our son has been anxious about be separated from his mother as he is reliant on her for all his food. The tiredness and anxiety restricts him from joining in sports with other children and leads to obesity. It doesn't help that most of the foods available for him to eat are either sugar or fat based.

Q8. In addition to our regular quarterly sessions with the local paediatrician and dietrician our son is also regulating seeing a child psychiatrist under the care of the local children mental health team. In the past he has regularly been referred to councillors, phycologists and even a hypnotist. He's had various stomach scans due to digestive pains. Our local school put a huge amount of resource into various plans to try and get him into school and eventually had to have him home schooled after successfully gaining an EHCP for him. We have had to now cover the costs of a small private school just to try and get him interacting with other children.

Q9. I don't believe they have considered how PKU effects different groups. I don't know how anyone with learning disabilities or cognitive impairment could manage this diet. If you can't speak English it would be impossible to follow diet, things as simple as reading the ingredients would be difficult. If we were on a low income our son wouldn't be at school. A women wanting to conceive would be very scared attempting to strictly control her phenylalanine level. If you are ill and can't stomach any food then your levels can rise dangerously through no fault of your own. Kuvan could help in so many ways.

Q10. Surely pregnant women have enough worry about without the added stress of what high protein levels might be doing to their unborn child. Every women has the right to conceive and that should be made as stress free as possible.
Research in the USA concludes when a pregnant woman’s phenylalanine levels get too high, they can cause serious problems in her baby, including:
Intellectual disabilities
Microcephaly.
Heart defects
Low birthweight

Q11. Anything that avoids any problems to an unborn baby must be a good thing.

Q12. *[no response given to this question]*

Q13. Please allow our son to access Kuvan now and for his whole adult life. It is incredibly hard to see how this rare condition can affect someone and their whole family so medically, mentally and emotionally. It would reduce the financial burden on the NHS in the long run due to severely reduced numbers of prescriptions, mental health assistance from NHS and his ability to be nearly normal in his eyes. Please.....

Respondent 43

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Once someone is accustomed to expanding their diet, how can you take this away when they reach 18 - it's not fair or makes sense. Please please please help to get Kuvan on NHS for under 18's and continue after their 18th birthday.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. Yes I agree, we find it incredibly difficult on a daily basis to explain about our son's condition to teachers and even going away on holiday is difficult. It's very hard for our son to explain this to his friends also. He has become very withdrawn coming up to his 12th birthday and is refusing to go out on his own with his friends without his family. He needs Kuvan to help him and to give him some confidence in what he can eat away from his family.

Q6. Yes, PKU not only effects our son, it has a massive impact on family members and friends.

Q7. Yes, I agree that there is a need for treatment to reduce PKU symptoms. We have noticed low moods and anxiety even on the strict diet. Our son has difficulty with focus as well.

Q8. If it comes down to costs and that's the only way we can get Kuvan, then we are willing to pay. We need help and guidance how to do this.

Q9. Any of the problems above and PKU must be difficult. PKU alone is very difficult and hard to manage without the added issues.

Q10. Kuvan should be offered to pregnant women at their risk.

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. Please give people the chance to see if they are compatible with Kuvan and help them to lead a normal life by taking Kuvan. Eating and drinking is a massive part of everyday life - it's everywhere you look - every other program on television is to do with food and eating out. If there's a chance that people can take Kuvan and join in with society then it should be provided.

Respondent 44

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. It would be incredibly difficult if not impossible and greatly traumatic for a young person to have to stop treatment with Kuvan when turning 18, 18 year olds used to a more relaxed diet would not have the coping skills to switch to a diet which is incredibly restricted and under any circumstances extremely difficult and emotionally traumatic to adhere to.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. NICE themselves have recognised that permanent harm to the brain can happen after the age of 18 if Phe levels are uncontrolled and too high. Many adults with PKU have serious symptoms caused by high Phe levels including cognitive issues such as memory problems, brain fog, mood problems, depression, heightened emotional state, aggression, psychosis and anxiety. Additionally they may suffer physical discomfort such as headaches and stomach issues, and have problems with disordered eating.

Q5. Yes, as a family member and carer of a child living with PKU, I can’t stress enough what a difference my nephew with PKU having a less restricted diet would make to the enormous stress and emotional upset our family goes through coping with his condition. Additionally this would be enormously helpful in lessening the burden of the practicalities of managing his PKU.

Q6. Yes, PKU impacts family members economically to a great degree, carers ability to work is significantly lessened as ensuring Phe levels are controlled by preparing and acquiring special food, and educating others like teachers, family and friends is time consuming. Additionally purchasing low protein foods is very expensive. My nephew is a PKU sufferer and his mother has to work less in order to cater for his needs, when I’m caring for him I also work less to ensure his food requirements are met.

Q7. I agree, these symptoms when Phe levels are high are extremely distressing for PKU sufferers and their carers to bare placing them under untold emotional stress, a treatment that alleviates this would therefore be invaluable and life changing for sufferers and their carers. My sister and her husband have noticed that when my nephew’s Phe levels are high his behaviour is far harder to manage.

Q8. Due to the reliance on a metabolic team to effectively manage the condition of PKU and the extra support needed from services such as schools and social services necessary to help sufferers and their carers cope with the debilitating symptoms and stresses of the condition significant costs are clearly incurred. A family member has already accessed counselling services at St Thomas’s Hospital and I have counselling. Extra support will be needed for my nephew when he starts school to ensure everything from kitchen staff to teachers are educated.

Information should be routinely collected on long term brain damage due to PKU, the number of children referred to early help services, social services and the costs involved. Evidence would then be available to estimate the effect on the quality of life of people with PKU. Kuvan could significantly improve the lives of individuals with PKU and their carers reducing the need to access some services.

Q9. No NICE has definitely not properly considered treating people fairly. Although they have recognised some people may find it harder to manage PKU through their diet and noted these disadvantaged groups they have not adequately included this in the cost analysis for the use of Kuvan in those 18 and over.
People with learning disabilities are more likely to be unable to control their Phe levels by dietary treatment, the help they require with this restricts their independence.

Q10. NICE should recommend Kuvan to help women manage Maternal PKU.

Q11. Despite recognising that controlling Phe levels in early pregnancy is important, ideally from before conception and that this would reduce the risk of Maternal PKU syndrome, NICE has failed to take this into account by deciding Kuvan is not cost effective in adults and the benefits of Kuvan in helping women with PKU have safe and happy pregnancies have been ignored.

Q12. NICE should include the costs of preventing neurological damage to the children of women with uncontrolled PKU. The effects of Maternal PKU on the fetus can be devastating, facial dysmorphism, microcephalic, intrauterine growth, retardation, developmental delay and congenital heart disease, resulting in life long conditions for these children and therefore greatly increased cost of care and requirement of support services.

Q13. Clinicians in the UK should be able to prescribe Kuvan within the range of 5mg/kg to 20mg/kg rather than the 10mg/kg dose NICE has recommended in order to allow them to prescribe the most helpful dose for their patients.

Respondent 45

Q1. No disagree, should be available to all people with PKU

Q2. Stopping Kuvan at the age of 18 (just as they are becoming adults) will be difficult to administer. On Kuvan they will have become more independent around food i.e. purchasing, preparing meals and eating out, this will then have to be completely reversed back to a very restricted diet with support.

Q3. I do not agree with NICE's view;There is a risk of long-term brain damage through high levels of phenylalanine as 'brain damage' is recognizable through headaches, depression, irritability, tiredness, poor decision making, etc.

Q4. My 24 year old daughter has all of the above symptoms and has been placed on anti-depressants by her GP to help with her anxiety and depression. She struggles at work and breaks down in tears quite a lot which results in her being sent home.

Q5. I can totally relate to the above statements, I reduced my working hours as a low protein diet involves more work than a normal diet from ordering/collection of prescriptions, shopping - constantly checking food labels, to preparing meals from scratch. I must add that I am no chef but I tried my best which caused unsurmountable arguments which ended up with either myself in tears or my daughter. She comes home hungry from work and therefore, insists that I do not prepare anything that she had not tried before, as this will instantly have a negative effect on her mood. She also complains about every meal being tomato based, she also went through a phase where she could not eat anything made from the low-protein flour as this was used for making bread, sausages, cakes, omelets, pancakes, etc and through time she became saturated with the flour products that she couldn't take anymore.

A less strict protein-restricted diet would enable my daughter to prepare meals for herself without constantly weighing out exchanges, enable her to socialize with family and friends. She is not interested in eating the food items which are not allowed on a restricted diet i.e. meat, fish, eggs, etc, all she wants is to be able to eat what she currently eats but without having to weigh out every meal.

Q6. PKU impacts our family massively from trying to get our GP to leave necessary items on repeat, to visiting numerous supermarkets to purchase their own brands, to constantly searching for foods with low-protein content and then paying an excessive amount for items.

Q7. It is not just children who have depression, anxiety, headaches, low moods, etc, my daughter is now an adult and experiences all of these on a daily basis. Does not socialize unless I am with her and cannot make a decision without asking me first. If we go shopping together I have tried to encourage her to ask for assistance or pay for items at the counter, she just can't do it, she will walk out of the shop.

Q8. 'Quality of life' - being able to have access to Kuvan is not just about being able to eat a normal diet it is predominately about reducing the elevated levels of phenylalanine in the brain to enable a better life, through better social, emotional, and physical wellbeing.

My daughter has told me the way she feels about her PKU has totally restricted her life in that she has had to create 2 personalities (1 without PKU and 1 with) she has been unable to tell people about her PKU, she just wants to feel good and to be able to raise her self-esteem about herself and to make decisions for herself.

Q9.

Kuvan should be made available to all groups as having PKU in itself is part of a disadvantage group due to the very restricted diet.

The PKU diet is a constant struggle not only to get levels down but to maintain is almost impossible without going hungry. When my daughter submits a blood sample to find they have not come down has a massive effect on her mood.

Q10. Kuvan should be made available to women who would like a family as being denied access to Kuvan may deter them from having children and could affect their relationships with their partners.

Q11. Kuvan should be made available to women with PKU who are wanting to plan a family, not after they have conceived which could cause harm to the baby.

Q12. Children born to women who have high levels of phenylalanine may be born with birth defect which will require assistance/support from social services

Q13. The PKU diet is a constant struggle not only to get levels down but to maintain is almost impossible without going hungry. When my daughter submits a blood sample to find they have not come down has a massive effect on her mood.

I constantly worry about my daughters levels which I know have an impact on her mental state of mind, she was so pleased when I informed her that Kuvan had been approved but then bitterly disappointed to find out that she was to old. I have been telling her for years hang on in there, they will find a treatment.

Her life is not just restricted by diet but her state of mind, her low self-esteem and not being able to socialize.

Respondent 46

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. This would be cruel to let someone live with the improvements given by Kuvan and then just take this away when they are 18.

Q3. NICE's statements are contradictory

Q4. No response.

Q5. Treatment allowing a less restricted diet would be great. When Abbie was a baby I was on the verge of post natal depression stressing about what she'd eat. I didn't trust anyone to look after her and feed her properly. Any carer, school professional etc given charge of a child with pku

needs to understand the diet, and the implications of what can happen if you don't adhere to it. The stress of keeping the person on track etc comes at a cost for the carer but actually benefits the government in the long run as a child with less affect on brain development etc won't need special education etc.

Q6. Yes they should have, a child with PKU affects all family members. Aunts, uncles, grannies and grandad. They all want to know what they need to do if they want to treat a child normally, and take for picnics / treats like any other child that is non PKU.

Q7. *[no response given to this question]*

Q8. Additional time is required when we start nursery. To work with the kitchen staff on a weekly basis to detail what we can have / amount of each food that Abbie could have. I've been very lucky that throughout primary school Abbie has had the same canteen staff. So we just spend time yearly with each teacher, every Brownie leader, Sunday school teacher and other parents of children that she visits. I don't count all the time I spend doing this but it is a factor daily. Arguing with your child about taking protein substitutes, eating food they shouldn't have, the list goes on.

Q9. Every person with PKU is affected differently. Families who on paper are the same could deal with things differently. One shoe doesn't fit all.

Q10. This is a crucial time in a woman's life so this would add stress worrying about an unborn child as well also.
I would recommend that Kuvan is offered to women with PKU of childbearing age or planning pregnancy.

Q11. I would recommend that Kuvan is offered to women with PKU of childbearing age or planning pregnancy.

Q12. No response.

Q13. *[no response given to this question]*

Respondent 47

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. It seems very unfeeling to stop a treatment which makes life easier, for a diet that is hard work, time consuming and less palatable

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. I recommend reading 'Sheila' by Anne Green

Q5. I agree

Q6. PKU affects every family member as each meal is different, needs separate prep and cooking time, and relies on being able to get the requested prescription items. Siblings get a lot less attention and could feel left out.

Q7. *[no response given to this question]*

Q8. *[no response given to this question]*

Q9. Everyone should have access to effective treatment.

Q10. NICE should recommend Kuvan be available to those women who would benefit. Just because there is no evidence is no excuse to perhaps cause damage by omission.

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 48

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. It would be incredibly difficult if not impossible and greatly traumatic for a young person to have to stop treatment with Kuvan when turning 18, 18 year olds used to a more relaxed diet would not have the coping skills to switch to a diet which is incredibly restricted and under any circumstances extremely difficult and emotionally traumatic to adhere to.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. NICE themselves have recognised that permanent harm to the brain can happen after the age of 18 if Phe levels are uncontrolled and too high. Many adults with PKU have serious symptoms caused by high Phe levels including cognitive issues such as memory problems, brain fog, mood problems, depression, heightened emotional state, aggression, psychosis and anxiety. Additionally they may suffer physical discomfort such as headaches and stomach issues, and have problems with disordered eating.

Q5. Yes, as a family member and carer of a child living with PKU, I can’t stress enough what a difference my grandson with PKU having a less restricted diet would make to the enormous stress and emotional upset our family goes through coping with his condition. Additionally this would be enormously helpful in lessening the burden of the practicalities of managing his PKU.

Q6. Yes, PKU impacts family members economically to a great degree, carers ability to work is significantly lessened as ensuring Phe levels are controlled by preparing and acquiring special food, and educating others like teachers, family and friends is time consuming. Additionally purchasing low protein foods is very expensive. My grandson is a PKU sufferer and his mother and father have to work less in order to cater for

his needs, when caring for him my other daughter also works less to ensure his food requirements are met. I incur extra costs to purchase suitable foods for his dietary needs.

Q7. I agree, these symptoms when Phe levels are high are extremely distressing for PKU sufferers and their carers to bare placing them under untold emotional stress, a treatment that alleviates this would therefore be invaluable and life changing for sufferers and their carers. My daughter and her husband have noticed that when my grandson's Phe levels are high his behaviour is far harder to manage.

Q8. Due to the reliance on a metabolic team to effectively manage the condition of PKU and the extra support needed from services such as schools and social services necessary to help sufferers and their carers cope with the debilitating symptoms and stresses of the condition significant costs are clearly incurred. A family member has already accessed counselling services at St Thomas's Hospital and my daughter also has counselling. Extra support will be needed when my grandson starts school this year to ensure everyone from kitchen staff to teachers are educated.

Information should be routinely collected on long term brain damage due to PKU, the number of children referred to early help services, social services and the costs involved. Evidence would then be available to estimate the effect on the quality of life of people with PKU. Kuvan could significantly improve the lives of individuals with PKU and their carers reducing the need to access some services.

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People with learning disabilities are more likely to be unable to control their Phe levels by dietary treatment, the help they require with this restricts their independence.

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Q13. Clinicians in the UK should be able to prescribe Kuvan within the range of 5mg/kg to 20mg/kg rather than the 10mg/kg dose NICE has recommended, in order to allow them to prescribe the most helpful dose for their patients.

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Q6. Yes NICE should have taken into account the impact on other family members when valuing treatments for PKU. PKU impacts family members economically to a great degree, carers ability to work is significantly lessened as ensuring Phe levels are controlled by preparing and acquiring special food, and educating others like teachers, family and friends is time consuming. Additionally purchasing low protein foods is very expensive. My grandson is a PKU sufferer and his mother and father have to work less in order to cater for his needs, when my other daughter is caring for him she also works less to ensure his food requirements are met. I incur extra costs buying foods suitable for his PKU condition which are expensive.

Q7. I agree, these symptoms when Phe levels are high are extremely distressing for PKU sufferers and their carers to bare placing them under untold emotional stress, a treatment that alleviates this would therefore be invaluable and life changing for sufferers and their carers. My daughter and her husband have noticed that when my grandson's Phe levels are high his behaviour is far harder to manage, this is very stressful, distressing and worrying for them.

Q8. Due to the reliance on a metabolic team to effectively manage the condition of PKU and the extra support needed from services such as schools and social services necessary to help sufferers and their carers cope with the debilitating symptoms and stresses of the condition significant costs are clearly incurred. A family member has already accessed counselling services at St Thomas's Hospital and my daughter also has counselling. Extra support will be needed when my grandson starts school this year to ensure everyone from kitchen staff to teachers are educated.

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Q13. Clinicians in the UK should be able to prescribe Kuvan within the range of 5mg/kg to 20mg/kg rather than the 10mg/kg dose NICE has recommended in order to allow them to prescribe the most helpful dose for their patients.

Respondent 50

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. To take away treatment at 18 is so damaging to an individuals mental health. To be accustomed to some sort of freedom with diet and then to have that taken away at 18 when PKU is a LIFE LONG condition is atrocious!!

Q3. I do not agree with NICE's view

Q4. *[no response given to this question]*

Q5. Yes I strongly Agree!! As a mother to a 6 year old with PKU I know first hand how time consuming and worrying the management of diet can be! The thought that goes into a day at school, a school trip a visit to a relative a party - this is every single day for the rest of their lives, PKU does not have a day off!! Therefore the pressure on parents and then the individual themselves as they get older is immense! The planning and restrictions with daily life will only get greater as the person ages. To have some kind of freedom with diet and to also gain the benefits that come along with kuvan eg) clearer mind less brain fog more focus less anxiety is so so welcomed!! You eat to live and survive healthily why should a person with PKU suffer just because they are born with a metabolic condition through no fault of their own.

Q6. Yes I do as a carer to a child with PKU kuvan is priceless! To be able to have a treatment for my daughter that will allow more freedom with diet & more clarity of mind would be amazing! To be able to eat just a small of amount of food from a menu in a restaurant and not have to take food alternatives with us would truly be life changing. I had always planned to have more than one child, but the effect mentally on caring for a child with PKU and the pressures that brings has made me make the decision to have no further children. I could have another child with PKU and knowing first hand what that entails I could not go through that again.

Q7. No I do not agree!! Knowing first hand how just a slight increase to normal PHE levels can effect my daughters mood her emotions her focus is immense. Her irritatability and lack of focus can really impact her daily life, her ability to take her medication and eat her protein exchanges her focus on school work. It really does effect this with just a slightly elavated PHE level

Q8. It absolutely does impact on quality of life!! To always be told you CAN'T eat that to be the only one taking medication x3 daily every SINGLE day. To never be able to order freely from a menu in a restaurant to eat at a buffet to drink whatever you want impacts your general quality of life immensely. Your relationship with food overall becomes a negative experience, increasing the temptation to not stick to diet therefore increasing PHE levels and all the knock effects that brings.

Q9. No they haven't considered treating PKU sufferers fairly. To expect a woman planning a family to stick to such a restrictive diet and to pallet all medication throughout is so unfair. To then expect that women once pregnant to continue this throughout pregnancy with nausea and the general ailments that come with pregnancy, whilst trying to do the best for their health and their unborn baby's health is also so unfair. People on low incomes or individuals with learning disabilities or autism etc etc do not need further stress in their lives when there human right as a living human being is to eat to live and survive, that being stripped away is quite frankly immoral.

Q10. I agree strongly with the recommendation to give Kuvan to maternal PKU surely a sound state of mind and a healthy relationship with food whilst growing a child is paramount.

Q11. I strongly welcome the use of kuvan for women either planning or at child bearing age. A healthy relationship with food that is enriched as much as possible with variety is strongly beneficial and is vital for giving the best chance of conception and a healthy pregnancy.

Q12. *[no response given to this question]*

Q13. PKU effects quality of life immensely. PKU is a life long condition there is no day off ever!! To strip away some freedom of diet more clarity of mind to impact so immensely on ones mental health purely because they've reached the age of 18 is dispicable!!! It is every human beings given right to eat to survive and be healthy. Why should a treatment that offers so much be taken away ever!! The brain does not stop growing or maturing at 18. Would the treatment for a diabetic be taken away when they become a so called adult?? To offer a treatment for a LIFE LONG metabolic condition that has no days off ever and then take that away just because an individual ages is immoral and so so WRONG!!!

Respondent 51

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I think it is wholly unethical to stop any treatment when someone turns a specific age. Stopping a treatment which effects someone's day to day life in such a dramatic way is cruel and callus. Having 2 children, a boy and a girl who have PKU, I understand what the day to day difficulties of eating the correct foods have upon the mental and physical health of a child. To restrict the foods consumed so dramatically and substituting with special low protein foods is extremely difficult. There is a skill to cooking low protein foods which I have had to learn as an adult. As an 18 year old, who potentially may be on Kuvan for almost their entire life and have eating a relaxed diet like their peers, to having to totally change their eating habits to such an extent because their medication have stopped, would be stressful, terrifying and life changing. The young adult (and also probably their parents) would need to learn how to cook the low protein foods, which foods can and cannot be eaten, finding a protein substitute which they can stomach and all this whilst at a vulnerable stage of their life ie: university, working, leaving home. Knowing that not all pregnancies are planned is also very worrying as a mother of a girl. A healthy lady having a baby is of no concern but, a lady with PKU who is having a baby has enormous consequences. Maintaining a very strict diet before getting pregnant and maintaining low blood Phe levels may not be possible if the pregnancy is unplanned. This would put both child and mother at risk of serious physical and mental health problems.

Q3. NICE's statements are contradictory

Q4. My Uncle was cared for by my Grandfather until his death. I understand the consequences of brain damage on both the individual and the family. My uncle was a happy and healthy young man until around the age of 18 years old when his health deteriorated. I saw first hand the effects this had on us as a family and if it had been preventable by taking medication. The brain damage that can occur from PKU is preventable.

Q5. I totally and fully agree with this statement.

Q6. I have drastically reduced my working hours to care for my children and ensure that they have enough food to eat by batch cooking meals on a given day as cooking foods from scratch takes a lot of time and effort

Q7. I fully agree with this statement and have had a number of mental health problems with my eldest child.

Q8. *[no response given to this question]*

Q9. We have a huge storage issue when it comes to the amount of prescription foods and protein substitute that we need to store. This is a real issue for us to the extent that we are having to convert out garage into storage space. We are lucky enough to be able to afford to do this and have the ability to do this.

Q10. The age of giving Kuvan should not be restricted.

Q11. The age of giving Kuvan should not be restricted.

Q12. This should have been included

Q13. I think that it is age discriminatory to remove the medication of a person based when they become 18 years old.

Respondent 52

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. No

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. Yes

Q5. Yes

Q6. Yes

Q7. Yes

Q8. Yes

Q9. No

Q10. Give them the tablet

Q11. I think Kuvan would give peace of mind to women of child bearing age with PKU.

Q12. All women of child bearing age should be given Kuan.

Q13. *[no response given to this question]*

Respondent 53

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. My daughter is prescribed Kuvan, and it’s completely liberalised her diet and her life. She couldn’t return to the PKU diet if she could no longer have Kuvan, as a family we no longer have to follow the strict regime of 4 supplements a day, all the PKU cooking and necessary abstinence

involved. She wouldn't be able to resist eating those foods she now eats everyday, without Kuvan she'd be off diet with the high blood/phe levels
It would also be a huge blow to her sense of self, self confidence and mental health to have to return to the PKU diet

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. I gave up a successful career to look after my daughters PKU. I don't have any extended family that could help. Now she's been prescribed Kuvan I've finally got the opportunity to return to work. Without kuvan I'd have to give that up again to help her manage her diet

Q6. I gave up my career to look after my daughter's PKU, I could have continued to be a contributing tax payer. Money lost to the Government through loss of taxes should be considered in their 'economic model'

Q7. The symptoms listed above in people with PKU should be treated. Kuvan is a treatment that reduces Phe in those that respond and therefore reduces the amount and frequency of those symptoms. Since my daughter has been taking Kuvan it's reduced the amount of stress in our household from my anxiety about keeping her phe levels within range to my daughters ability to appear normal in front of her peers. She's become more outgoing, we're able to visit restaurants without meltdowns. I can't exaggerate the positive effect Kuvan has had on our family

Q8. *[no response given to this question]*

Q9. It's inherently unfair to exclude some of the PKU population from treatment, while allowing it to others, and then take it off those who are allowed it at a later date

Q10. I hope the NSPKU has some proof to forward to NICE about this. My understanding is that phe levels are even harder to control in pregnancy due to the growing foetus and its changing requirements for nourishment, if they aren't controlled the unborn baby is irreversibly brain damaged. Kuvan should be made available to pregnant PKU mums

Q11. My understanding is that PKU women who are planning pregnancy need to have phe levels within range before becoming pregnant. Many PKU women are off diet and find it incredibly difficult to return to diet for pregnancy. Some become pregnant accidentally while they're off diet, thereby damaging the unborn baby. If adults were already taking Kuvan it would reduce the risk to the unborn child

Q12. The cost to the government of a brain damaged child born to a PKU mum, because she was off diet is enormous. It's likely that the child, at some point, will need care beyond what the family could provide and may need to be institutionalised

Q13. My daughter is prescribed Kuvan through an IFR because she has other medical problems that were negatively impacted by her PKU, she's 14yrs old

She has severe PKU, before Kuvan she was on between 4 to 7 grams of protein per day. The equivalent of a slice of bread.
She was only allowed fruit and some veg, small measured quantities of potato and rice.
She had to drink nearly half a litre of a highly unpalatable artificial supplement, which provided 95%+ of her nutrition.
Most of her food, pasta, bread, crispbreads, burgers, sausages, crisps, biscuits, cakes and flour were on prescription

The flour, a key prescription ingredient for making PKU bread and other basic foods is incredibly difficult to work with. Often recipes failed, were inedible and thrown away, a waste of NHS money

No one, including us expected Kuvan to work for her.
My daughter's response to Kuvan exceeded everyones expectations, including her metabolic team. She's now able to tolerate 40 exchanges per day and keep within the recommended phe range.

This meant that we stopped using all prescription products* a huge cost saving to the NHS
My daughter has saved the NHS money by
cutting her intake of supplements by 80%
reducing her use of prescription products by 100%
no appointments/drugs needed for her PKU induced BMD from endocrinology**

You might think that being brought up on artificial supplements and artificial prescription food a person with PKU might not know or want anything different but this wasn't true. My daughter preferred everything about our food, sometimes she would beg for tiny scraps and crumbs left on our plates. Now she can buy a sandwich off the shelf and eat it, amazing.
Her life and ours has changed inconceivably for the better since Kuvan

*The only caveat to this is she has one small size PKU supplement per day, a precautionary measure by her dietician for two reasons. My daughter's response to Kuvan was a surprise, and new territory for her medical team, it was thought wise to keep her on one small supplement to cover for any shortfall.

*eating more natural protein through taking Kuvan restored her BMD from osteopenia levels too normal

Respondent 54

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. An abrupt end to medication at 18 could be detrimental particularly to those people who struggle to control PKU through their diet. Older teenagers and adults can be adverse to anything which restricts their freedoms and pregnant women and their babies would be at particular and considerable risk.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. the need to be constantly vigil and on guard places a considerable burden on carers.

Q6. Yes

Q7. I fully concur that any treatment that reduces PKU symptoms is invaluable.

Q8. Lack of evidence is not proof that extra services and costs are not being incurred by support services, money spent on medication will alleviate these already stretched services.

Q9. It is obvious that the vulnerable and pregnant women will suffer hugely if access to medication is terminated at age 18.

Q10. Protection of unborn children should be a priority in any decision regarding treatments

Q11. As above.

Q12. It would seem likely the cost associated with neurological damage to children of PKU sufferers could be high both financially and emotionally and should be a priority consideration when deciding who to treat and for how long with Kuvan

Q13. PKU is a condition which places a considerable burden on families and patients as the consequences of failing to treat and control symptoms through diet are irreversible and life altering. Any drug which helps alleviate the risk of mismanagement is of vital importance to those living with PKU and I believe it should be prescribed for all patients in need regardless of age and with no restrictions on the dose available.

Respondent 55

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Making diet stricter at 18 is a dreadful idea! This is just the time they are going out into the world and want to lead as normal a life as possible with their peer group.
Also what about maternal PKU?
My daughter would have benefitted greatly if she could have had more than her 1-2 exchanges a day. Suffered greatly with sickness and had two miscarriages.

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. When my daughter was a child she was never cared for by anyone other than my husband or myself as we felt it was unfair to expect other people to have to be responsible for her diet and subsequent wellbeing.
If her diet had been less restricted we would have suffered less stress. It is possible I might have considered returning to work instead of just getting a Saturday job when my husband was available to look after her.

Q6. *[no response given to this question]*

Q7. Being tired seems to have continued into adulthood. Also headaches. Needing anti-depressants following miscarriage is still ongoing.

Q8. *[no response given to this question]*

Q9. Surely anyone who has PKU should be entitled to the best possible treatment available.

Q10. NICE should TOTALLY recommend Kuvan to help women with PKU to have the best possible outcome with their pregnancies.
My daughter had two miscarriages after having struggled with only 1-2 protein exchanges a day to try to keep her levels down. She was suffering from severe sickness and anything that had helped her to having something like a normal pregnancy and outcome would have been so welcome.

Q11. As you have to have a very restricted protein intake during the time you are planning to conceive anything to help during this stressful time would be helpful

Q12. *[no response given to this question]*

Q13. It would have been wonderful to have had a more relaxed approach to my daughter's diet as a child but having seen her go through university and adult life it would have been very unfair to have had any relaxation of diet taken away at 18.

Respondent 56

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I think stopping Kuvan at 18 is unfair, children will get used to certain way of eating. Then when life is starting to change quite significantly, such as going off to university, you are expecting young adults to have to change their entire way of eating again.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. I completely agree with this statement. The mother of the child I teach has had to be extremely close contact with the school, all the staff who teach her child and the catering staff. ******** is given her own menu and we have a book that goes from home to school each day where we write down what exchanges she has eaten. As her teacher I have to be aware of everything she is eating and if we were to do baking in school we want ******** not to feel different so everything has to be carefully worked out. We are fortunate to be in a smaller school where this is easier to manage but should ******** need to go to a larger school my concerns that the importance of her diet would get overlooked. I have read about PKU and understand the significance of her dietary requirements but not everyone would take the same level of care I do. If ******** was able to be on a less strict protein-restricted diet it would make life a lot easier for her and allow for a greater freedom. Currently she can't stay at grandparents or go over to children's houses for tea unless her parents have given her a packed lunch.

Q6. Yes the cost of a PKU diet can be very expensive, which can also make it unfair for disadvantaged families to have the correct access to the right types of food

Q7. Yes, this can be quite evident in the pupil I teach, particularly the lack of focus. This is likely to have a detrimental effect on her school work as she gets older.

Q8. *[no response given to this question]*

Q9. Everybody should have the right to food which is nutritious to them

Q10. I think there is evidence to show contrary to this and that there would be benefits to a mother and unborn child to have a higher protein diet. Therefore, I believe it would be wise for women trying to conceive and those who are pregnant to be given Kuvan.

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 57

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. According to NICE, the aim is to improve outcomes for people. Access to Kuvan for children with PKU would certainly achieve this. However, stopping access at age 18 would undo all that good work. The transition into adulthood, which is only really beginning for many at 18, is difficult for everybody, but this struggle would be made too difficult for many if their lifeline (Kuvan) is taken away. This would then have a huge impact upon, not only the person following the PKU diet, but also their family, friends and the wider community.

At age 18, many people become more independent and often live on their own for the first time. Removal of Kuvan would certainly cripple PKU sufferers and stifle their ability to function at a healthy level. It would make it harder to get a job or continue higher education.

Increasing the difficulty and making the PKU diet harder to manage at this time would have a negative impact upon PKU sufferers mental and physical health. This would then require further support from health professionals, families etc.

A big question I ask, is whether Kuvan would be reduced gradually as people approach 18 years of age or whether it would be cut off completely on the 18th birthday. Is there any evidence or research into how Kuvan should be reduced or stopped?

Q3. NICE's statements are contradictory

Q4. It is clear that NICE's comments on brain development (which continues to age 25) and the fact they say there is risk of brain damage in adults. High phenylalanine levels produce symptoms such as seizures, metal health issues and mental cognition difficulties.

It feels very strange to try to explain why the above difficulties should be avoided. To simplify my argument that Kuvan (and any other treatment for PKU) should be available for life, I wish for decision-makers to consider whether the removal of Kuvan moves PKU patients closer to mental and physical well-being or closer to mental and physical problems. Even NICE's guidance in this instance suggests the latter. It is frankly disgusting to suggest that any effective treatment should be given and then taken away, but the risks with mismanagement of PKU are huge. A negative effect on one person would be a tragedy, however, if the current recommendations stay in place, the majority of people affected will face huge struggles with their mental and physical health.

Q5. The availability of a treatment which allows a less strict protein-restricted diet would a hugely positive thing for my PKU patients, their family, friends and/ or carers.

Every person who cares for a young person and guides them through life needs to make positive choices to promote their health and happiness. The PKU diet strangles the freedom to make positive choices. When a PKU parent/ carer experiences a difficulty with the management of the PKU diet, they do not see the problem in front of them, they see the next 10 years of dealing with that problem. The risks are huge and the potential negative impact that goes alongside poor management of the PKU diet puts an incredible strain on PKU parents/ carers. Removing access to Kuvan, or other effective treatments, at age 18 would put extra pressure on parents/ carers.

Access to Kuvan up to age 18 would increase PKU patients' ability to manage their diet as effectively as possible throughout their childhood. To improve outcomes, the most appropriate treatment should continue to be available throughout every PKU patient's adult life.

For PKU parents/ carers to have the worry of treatment being removed hanging over them is a huge amount of pressure. This will undoubtedly impact negatively upon their health and wellbeing.

Q6. NICE should have taken into account the impact of PKU on other family members when valuing treatments for PKU. PKU parents/ carers and family members change their life to better suit a person they care for when they have PKU.

The current guidance sets people up to fail. The burden of this failure will be carried by PKU parents/ carers and family members. The problems they face, when appropriate treatments are removed, will have been avoidable. This in turn would lead to costs in other areas for the NHS.

Q7. People with PKU and/ or their parents/ carers will gain a certain peace of mind over blood Phe levels should access to Kuvan, or another appropriate treatment, become available. However, the worry and stress of the approaching removal of an effective treatment will undo any potential peace of mind. Worrying about this would likely outweigh the positives. If you know additional and unneeded problems and pressure are imminent, you will struggle with that burden.

Allowing access and taking it away, it senseless from a patient care point of view. Especially when the potential negative effects are so extreme and scary.

Having to articulate a coherent argument when the potential difficulties associated with PKU are just ahead, is not easy. If compassion was part of the decision making process, then the best treatments, i.e. Kuvan, would be made available for life. Anything less is contradictory to NICE's aim to provide access to high quality care and good outcomes for people.

Q8. NICE guidance feeds into how the NHS delivers health care. The NHS aims to give people consistently safe, high quality, compassionate care. Removal of an effective treatment for a condition, which is extremely hard to manage, puts extra pressure on other services, such as education and social services. NICE guidance should aim to avoid amplifying problems for other services. The removal of Kuvan, and other appropriate treatments will increase costs and pressure on other services. This extra cost and pressure is avoidable.

Q9. NICE said some people may have greater difficulty managing PKU through diet. NICE have said the groups of people who may be disadvantaged include - "People who face such difficulties include: people with a learning disability, sensory impairment, or cognitive impairment• autistic people and people with comorbidities such as diabetes and gut disorders• people on low incomes, living in poor or in insecure housing• certain ethnic groups including people who do not speak English and Gypsy, Roma and Traveller communities• people in social care settings• women with PKU who need to establish controlled phenylalanine levels before conception to avoid damage to the unborn baby.

People affected by any of the above may need extra support with the management of the PKU diet. NICE have not properly considered how best to achieve appropriate care and support for specific groups.

Q10. PKU is even more difficult to manage during pregnancy. Kuvan would make pregnancy more manageable.

Kuvan should be available to pregnant women with PKU. Kuvan should be available to all adults with PKU.

Q11. NICE should seek to utilize patient experiences to inform decision making for the use of Kuvan during pregnancy and throughout all adulthood.

Q12. Kuvan helps avoid neurological damage. If it is available and appropriate, it should be used to treat anyone who may benefit.

Q13. NICE needs to make Kuvan, and any other effective treatments, available for PKU patients throughout the whole of their lives.

Devaluing peoples' lives and experiences by withholding effective treatments for potentially devastating conditions, such as PKU, should be avoided by NICE.

I strongly urge NICE to recommend access to Kuvan for everyone who may benefit (for their whole life).

Respondent 58

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Pku is a life long condition therefore medication should also be life long. The diet is limiting & very hard to manage.

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. The strain PKU puts on a family is huge. We as grandparents can’t even just take our granddaughter out for the day without instructions, measured food & a must if do’s and don’t’s

Q6. Kuvan could be life changing to many and to families this is priceless.

Q7. My 6 year old granddaughter does struggle with her learning at school & lacks good concentration levels.

Q8. *[no response given to this question]*

Q9. Pku is a life long condition treatment should also be lifelong. There is no price on quality of life & everyone should be entitled to live to the best quality available

Q10. The medication should absolutely be available to women who are trying to convince (along with every person who has Pku) to prevent harm to their unborn child.

Q11. It is essential that this drug be available to everyone who has Pku no none should be discriminated & if that were the case women trying to conceive would already be on the medication.

Q12. *[no response given to this question]*

Q13. The drug should it be capped at 10mg when we know the response rate is between 10-20mg. Only 30% of Pku patients currently respond to the medication so by capping it surly this response rate will fall even lower.

Respondent 59

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. The medication should not be taken away at 18, Pku is a lifelong condition to take it away when a child hits adulthood & becomes responsible for themselves is inhumane. The diet is very hard to live with.

Q3. NICE's statements are contradictory

Q4. Your brain never stops developing event in to adulthood.

Q5. Unless you are the parent of a Pku child it's hard to understand the additional stress & care that is needed. I as a grandparent can't even take my granddaughter out for the day without a list of instructions, weighed and measure food, along with supplements & a list of what we can & can't have. This makes support for the parents very limited.

Q6. Yes

Q7. A medication that could enhance my daughters schooling experience by allowing her to feel less tired & have more focus could be life changing for her future. Clearly kuvan is so much more than simply the food you can have on your plate.

Q8. Children with Pku & there early years learning experiences should be monitored more closely as it is becoming clear that more support for many is required. Kuvan has proved it can help with a Pku patients ability to concentrate and in return learn.

Q9. No one should be discriminated all children & adults with Pku should have access to the medication

Q10. If a medication can support the mental & physical health outcome of an unborn child it would be ludicrous for it not to be available.

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. The medication cap of 10mg needs to be upped to 20mg - we already know the resolve rate is relatively low at about 30% and that people respond on a dose between 10-20mg to cap the dose will further lower the response rate. Everyone should be entitled to a fair chance at responding to kuvan.

Respondent 60

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. This is not a good proposal, to expect an 18 year old to switch to diet which is very difficult to comply with after using Kuvan for their childhood is unrealistic. At 18 children are starting to become independent, and the ones going to university would find the change in diet on top of all other changes that occur at that time to be extremely stressful - they would not be able to cope with this pressure and most likely not be able to control their Phe levels correctly.

Q3. I do not agree with this view, the brain is continuously changing as we get older and lifelong learning is vital for long healthy lifestyle

Q4. Our daughter is 20 years old and by being on a very good controlled diet I do not have knowledge or experience of long term brain damage in adults.

Q5. Yes this defiantly has had a negative effect on our family - it took me many years to learn to make palatable foods with limited ingredients, and the process of managing PKU, my daughter's refusal to comply with the diet and keeping her blood levels in the safe range was so time consuming and stressful that my wife had to give up full time work to ensure that she was kept safe and fed safely.

Q6. Defiantly they should - my wife had to give up full time work to ensure that our daughter was kept safe and fed safely.

Q7. My daughter is 20, has PKU and is studying at university. She has been diagnosed with specific learning difficulties and slow processing. She needs extra support and extra time because she cannot absorb or process the information she reads and suffers from brain fog. She suffers from anxiety which stops her from doing some of the things she wants to do, such as applying for part-time jobs. She has a tremor which affects her ability to carry out the practical side of the course. She lives in fear that these problems will only get worse and will affect her career options and future. Her PKU consultant has referred her to neurology to assess the extent of the problem. These effects are common in people with PKU.

Q8. We have incurred the following costs:
>> DLA / PIP (higher rate)
>> Disabled Student Allowance - £3500 per year
>> Extra literacy support throughout school
>> Extra PKU consultations with metabolic team
>> Gastroenterology investigation
>> Neurology investigation
>> Additional GP appointments
>> Referral to Mental Health Team for anxiety
>> Prescriptions for four different laxatives
>> Consultations with clinical psychologist for behavioural issues

Q9. NICE have not properly considered treating people fairly - why stop Kuvan at 18? this is discriminatory, they should provide as much support to vulnerable population to reduce the effect of brain damage for people with PKU - from whatever community they live in.

Q10. Another unfair proposal, PKU women of child bearing age should have all the support they need to manage the diet and provide the best start for the unborn child.

Q11. PKU women of child bearing age should have all the support they need to manage the diet and provide the best start for the unborn child; if this can be enhanced with Kuvan then it makes no sense to stop at 18.

Q12. My 20 year old daughter has already said that she is afraid to consider pregnancy and will probably not have children. She is afraid of the damage that her PKU will do to the unborn child and understands that it is very difficult to keep levels in the safe range for pregnancy, having spoken to women who have gone through this. She is anxious anyway and knows that the anxiety of pregnancy with PKU will be too much for her to bear.

Q13. PKU is a condition for life and the 'diet' is for life. It makes no sense to treat only for 18 years and then stop treating. It is cruel and unfair.
NICE is not treating people with PKU equally by making this decision.
They has not given enough consideration to the realities and lived experience of those adults living with PKU.
Most other European countries - and many other countries around the world - understand the difficulty of living with PKU and prescribe Kuvan for children and adults, knowing that it will enhance their quality of life and allow them to be productive and contented citizens. It is very hard to understand why NICE does not value the quality of life of ALL people with PKU.

Respondent 61

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. While I am extremely pleased that Sapropterin has been recommended for children it is absolutely crazy to suggest that a potentially life changing treatment should suddenly be withdrawn at the age of 18. It is effectively a cliff edge for both teenagers who are on the treatment and for their families knowing that the treatment will suddenly stop. Our son is nearly 4 years old and so far the dietary challenges around PKU have rested predominantly with us as we have tried to navigate the diet, the weekly blood spot assessments and it has been an emotional rollercoaster already. But we have yet to reach the years when our son goes to school and has the freedom to choose what he eats and becomes fully aware of the impact of PKU on his life. Talking to other families at PKU events we are aware that as children get older and they become more responsible for their own choices there are many additional challenges they face. These include managing their own diet and the fallout of falling off the diet but also coming to terms with the fact that they are different when all they want to do is fit in and be the same as their peers. Teenage years are volatile and confusing at best and as parents our job is to support and prepare our children for life on their own. This will including supporting them mentally and emotionally but also practically so they have the skills to look after themselves. A persons diet is such a fundamental part of any daily life and with the PKU diet being so strict it requires us to work really hard to find particular foods and meals that work for our son as an individual and the whole family to support him. From our experience we believe the only way to approach this is by reinforcing good habits around food and having a positive attitude towards the diet. It takes lots and lots of practice and reinforcement. This is the messages we intend to pass onto our son as he grows older. Sapropterin could offer our son a better quality of life with reduced anxiety and aggression (signs of which we can already see arising at the age of 3 years old), improved concentration and cognitive function and where he can become accustomed to a diet with more normal foods. To know that this could all be taken away at the age of 18 is lunacy and makes going onto the treatment in the first place a difficult decision particularly for older children who may only get to experience a few short years of improved life experience. You are effectively asking young adults and they families to go back to the drawing board, abandoning years of practice and hard earned positive habits and start rebuilding new tougher habits from scratch with a severally more restricted diet while also dealing with the additional mental issues such as anxiety, aggression and depression which the treatment also addresses and the fallout of this could be catastrophic. I believe it is highly likely as soon as they come of the treatment they will not be able to stay on the diet and the potential risk of long term brain damage in adulthood from high levels of Phe alongside the inevitable mental health issues that will arise means that the withdrawal of the treatment is unacceptable. The diet is for life not just while you are young.

Q3. NICE's statements are contradictory

Q4. I do not have any first hand experience or extensive knowledge about the potential for long term brain damage but I also feel there is not enough evidence to say that long term brain damage can not occur if you fall off the diet once you reach adult hood. It is my understanding the the brain continues to develop into the 80s and 90s and it doesn't just stop at at the age of 25 as the consultation states. No one in the PKU community or the doctors we have talked to has said that falling off the diet and increasing Phe levels over a long period of time as an adult would categorically not cause brain damage and we have been told that it does have other very real and negative impacts on behaviour and mental health.

Q5. From the moment we received the diagnosis our lives weren't the same. While we have started to learn to live with the diet it has been very challenging and stressful at times. We are lucky to have the support of the Evelina hospital where specialist doctors and dieticians understand the condition. But beyond that support network you are very much left to your own devices and it can be extremely daunting. We rely on medical food which needs to be ordered each month and there are so many hoops to jump through just to get a packet of medicated pasta or hot breakfast. It all takes time and chasing up. Sending prescriptions to doctors surgeries to send to the company providing then product who deliver it to a different chemist. The process is not smooth and it can take weeks and months to get the food we ordered and some time not at all. We have to call doctors to chase prescriptions and pharmacist to check if things have arrived and on a number of occasions our orders have just got lost in system. As I say all of this takes time and causes stress. I know a number of people in the PKU community (ourselves included) got quite a bit of anxiety around the whole Brexit build up not know if the supply chains would allow us to continue to receive the supplements and foods we needed for our son.

We have worries about when our son goes to school and whether the school can support him with his diet when he gain more freedom to choose what he eats. We've had to spend lots of time educating nursery settings about PKU what it is and how they can help support our son.

If his diet was less strict the pressure on all of the areas above would be reduces and I think families and carers across the board would be less stressed and gain more time to care for their children with and without PKU in other ways as a result.

Q6. Time and worry is a massive factor for family members and extended family members of children with PKU. As mentioned previously about the amount of time taken to chase prescriptions there is also a lot of time spent planning meals, buying more expensive ingredients, making packed lunches and preparing things from scratch that you could otherwise buy from a shop so that a child with PKU has an alternative to what their siblings have. Cheaper convenient foods are generally not an option. In additional hospital visits, blood spots all have an impact on time and I believe when children get older and anxiety, concentration issues and gastric issues come in to play the economic impact of families only increases. I have heard cases from other families where children have had to have time off school due to anxiety and gastric issues and parents and carers have had to take time off work as a result.

Q7. Our son is only 3 years old so I don't have much first hand experience of some of the issues that I have heard impact other families. I have heard account from other parents of difficulty with focus, depression or anxiety, gastric issues, headaches, fatigue and aggressiveness due to high Phe levels. With a young child who can't communicate like an older child it is sometimes difficult to assess what is a result of Phe levels and what is other factors but I would say we already see in our 3 year old signs of high levels of aggression and difficulties with mood/behaviour. We are very interested in Sapropterin/Kuvans ability to bring improvements in these harder to diagnose areas.

Q8. Because the condition is so rare and there aren't large numbers of people to assess I understand it is hard to quantify the impact PKU has on people and their families and support networks. We are early on in our journey but it already has a significant impact on our time and energy, which also has a result on us financially. We would urge more people to come forward with their stories so a better picture can be painted of the impact of the condition and its wider ramifications.

Q9. I think the cost implicating for the NHS of removing the treatment at the age of 18 will be huge as they will be setting people up to fail. There will be a huge spike in cases of anxiety, depression as many people fail to adjust to the stricter change in diet and get increased Phe levels as a result. As the brain continues to develop after 18 this is likely to result in increased cases of long term brain damage which will cost the NHS and in turn this will have an economic impact too as healthy functional members of society become ineffective or unable to work. It is also surely discriminatory to prevent access to a treatment based on age, disability, ethnicity, income levels or gender (in the case of concerns over funding treatment for women trying to conceive).

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. One other issue is regards to regulating dosages of treatment. There needs to be flexibility in the dosages administered. Different people respond to different dosages. Some people may respond to lower dosages than are being recommended but some will need slightly higher dosages. Generally it is my understanding that it can be anywhere from 5-20mg/day but the putting a hard and fast restriction on a particular dosage that everyone needs to adhere to is not going to work. The medics must be given flexibility to administer with in a realistic range so the majority of patients have the chance to respond to the treatment. In reality because it is a law of averages I don't believe this will have much of a financial impact but will allow many more people to experience the advantage of the treatment.

Respondent 62

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Nice are obviously not aware of the problems of sticking to a low protein diet. It is callous to make an arbitrary date based on cost, at which point a young adult, having to learn to cope with living more independently also has to adhere to a more limited diet. I would like the people who are making the decisions to try a low protein diet for a few weeks and see if their viewpoint changed at all.

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. Based on my own experience as a mother with a son with pku, it has been an incredibly stressful experience supporting him to maintain his diet. It continues to be so even though he is now 19. It is a permanent source of stress that while the current system is maintained will continue.

Q6. I definitely think that Nice should take into account the impact of PKU on the family. It has been an additional job taking care of our son. This has reduced our ability to progress in our careers though lack of time and the stress of knowing what would happen to him if he didn't have our support. This will have an impact on the future when we retire. We face a poor retirement due to PKU and will have to work longer than is healthy.

Q7. I agree.

Q8. In *******'s early years I had a lot of support from the dietician's at BCH. **** was refusing his supplement and had to be admitted to hospital to help us be able to feed it to him. I cannot tell you how horrible it is to have to learn to force feed your child. I used to speak to the dieticians regularly after ours. As a result of the struggles we had maintaining ****'s diet, our social life suffered. Events like this have contributed to me suffering from anxiety and depression in later years. It is still costing the NHS money to support me.

Q9. I know of PKU families who were so ashamed that their child had PKU that they wouldn't allow them to eat the diet in public. That lead to the child not being able to stick to the diet. The outcome for these children was sad. Anything that allows a more natural diet should be considered for all ages and cultures.

Q10. I think that this is one instance where the research needs to follow after it has been prescribed. Woman with PKU should be given the choice to have anything that is medically safe that would make their lives less stressful. I think that NICE should give pregnant woman the choice and research the results.

Q11. Give woman with PKU the choice.

Q12. Include the costs.

Q13. I hope that NICE start to realise that behind their recommendations are people with PKU who have an incredible disadvantage from birth. People with cancer get prescribed very expensive drugs that may only prolong their lives for months. I am not saying that they shouldn't. I am saying that people with PKU should receive any safe alternatives to the incredibly strict diet to allow them to reach their maximum potential in life. What price improved outcomes for a very small part of the population and their families?

Respondent 63

Q1. I think that NICE should look at giving all people with PKU peg pal.

Q2. No because all people with PKU should have access to peg pal as they do in America and Europe.

Q3. NICE's statements are contradictory

Q4. no

Q5. I do not welcome this treatment. As a mother of a 20 year old with classic PKU I do not agree as this treatment would not be effective for him.

Q6. I do think that Nice should take into account the impact of PKU on other family members when valuing treatments for PKU. However, when is peg pal going to be considered?

Q7. I agree that there is a need for a treatment that can reduce PKU symptoms etc. However, my son's PKU is not treatable with Kuvan. What is going to happen to children and adults with the much more serious classic PKU? When is Nice going to authorise peg pal for use in the UK?

Q8. I am happy to provide you with plenty of evidence of the effect on the quality of life of people with PKU as I am sure my son it. If he had access to the peg pal treatment it would transform his life.

Q9. No.

Q10. To authorise peg pal to be a treatment for classic PKU in the UK and funded by the NHS.

Q11. How many women with PKU of child bearing age will be able to use Kuvan compared to peg pal? Are NICE discriminating against the more severe form of PKU?

Q12. *[no response given to this question]*

Q13. My son has classic PKU. I completed a form earlier. I would like you to disregard the earlier form in favour of this one. After I completed the form, I spoke to my son. This form better reflects my own views which, after discussion with my son, will be the start of me campaigning to make sure that both children and adults with classic PKU receive peg pal on the NHS if they wish.

Respondent 64

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I think that it is unethical to stop treatment of kuvan at the age of 18 and it is discriminating against adults with pku. As much as I would welcome the opportunity for our son to have access to kuvan, I would be highly concerned that the support and freedoms kuvan would enable him to have as a teenager and then for it to be taken away as soon as he turns 18 would be detrimental to his mental heath. Our son already struggles with having pku, he suffers with anxiety and is extremely frustrated at how much having pku inhibits him from having the freedoms of any other child of his age. Having access to a treatment that would enable our son to have more protein exchanges would be life changing for him and for us as a family. Catering for the pku diet is a long and arduous task. It requires precise measuring, lots of preparation and careful planning, something that is hard to do as a parent let alone an adult that has pku and has to hold down a job at the same time. The implications and restrictions pku has on lives effects every aspect of development, especially social and emotional development not only to the pku sufferer but alos to their family members. The unpalatable protein substitutes and the processed manufactured prescription foods are not easy to live off when you have very little protein allowance in your diet, it is something our son struggles with on a daily basis and will continue to struggle with for the rest of his life if he is not given fair and equal treatment to medications that can help him to have a better quality of life for all of his life.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. I find this statement both ill-informed and contradictory. To quote nice 'brain development does not stop until around age 25' if this is the information they have based their decision on then why are they suggesting stopping treatment at 18 and not at 25. The age of 18 upwards is when young adults are at college and universities and the workloads they have are immense, they are transitioning into adulthood and becoming more independent. This is the time in their lives where they will have to start managing their own diets and if they have had access to kuvan and a less restrictive diet nice are suggestion that they should have the treatment taken away and learn to cope with more restrictions whilst maturing into young adults. This is the ages where social development becomes more prevalent and if they are then expected to have more limitations on how they can socialise (lets face it food is at the centre of every social activity), this can have a devastating affect on their mental heath and they could become more withdrawn from social events.
The information that they have based their opinions on is lacking any evidence, to quote a paragraph from Alexis Wnuk a scientific writer and editor for BrainFacts.org 'intelligence involves many different cognitive abilities, each of which develops on its own timescale. Fluid intelligence, which includes abilities like solving problems and identifying patterns, peaks at around 3o. By contrast, crystallized intelligence, which deals with vocabulary and knowledge of facts, increases until about age 50.There may not be a single point in adulthood at which all or even most of our cognitive functions operate at peak performance'
By allowing access to medication and taking it away at 18 nice are using age discrimination and are not enabling each individual to reach there full cognitive potential.
To quote findings from a placebo- controlled crossover trial. 'High phenylalanine levels directly affect mood and sustained attention in adults with phenylketonuria'.

If nice have said there is not enough evidence to support giving kuvan to adults then maybe they should do more research starting with listening to adults with pku and the troubles they face daily.

Q5. Yes I agree that there is an additional strain on carers of children with pku and that managing the dietary treatment is stressful and time consuming. My own career has suffered as a result as when my maternity leave was nearing its end, I looked for nursery places and there was no local nurseries that would accept my son as they stated they couldn't give that much time and attention to 1 child. As our son got older it was apparent that working full time and managing the his strict diet was not going to be possible.
As parents of a child with pku we feel added overwhelming pressures and constant worries relating to pku and these outweigh any pressures that a 'normal' child's parents face.
The difficult transition to allow your child to grow and have more freedoms for any pku parent bring their own added anxieties and concerns.
Because pku is a rare disability everyone new that our son has contact with needs to be given the full information on how they need to cater for his needs whilst in their care as its always the first time they have ever heard of the condition.
We have had instances in hospital where heath care professional's have administered the incorrect medication when our son has been admitted to hospital for non pku related issues.
This caused dangerously high phenylalanine levels and we had to have intense involvement with our sons metabolic team in order to get the phe levels stable.
We have had to have numerous meetings with school staff to ensure they completely understand the consequences of our sons condition and the role in which they need to play to ensure his levels are maintained.
However hard the people involved in our sons care, mistakes have been made along the way and this leads to added anxieties and distrust of peoples understanding or acknowledgment. It is harder to meet the needs of a disability when you can physically see it.
Pku has not only had an effect on our sons mental health but also on my own as his main carer.

Q6. I don't feel that nice understand the actual restrictions and negative associations that people with pku and their family members have. Our son is very resentful of his pku and his stuggles impact on our family as a whole. But its not just children's family's that struggle. Many pku adults family's struggle to understand how hard it is to actually have pku and this can lead to growing resentments.
Having access to any treatment that would ease the burned of pku on our son and our family would be life changing for us all. Just being able to have more protein in his diet would allow him, and us the freedoms to be able to live a more 'normal' life where not every single thing has to be regimentally planned. Where we can go on spur of the moment trips out, knowing that we can stop off at any pub or restaurant for a meal and there will be things on the menu that our son could have would release pressures and anxieties that we have to deal with daily. This will be the same for adults with pku who feel that they hold their families back because of their condition.
To someone without knowledge of pku, food is often taken for granted but when you have such a restricted diet and your freedom of food choice is taken away it can have a devastating effect on your relationship to food and often leads to eating disorders and social and emotional development problems.

Q7. I agree that pku has related symptoms and side effects of high phenylalanine and we have had first hand experience of this. A a younger child our son experienced night terrors when he had high phe levels, to this day he still has a poorer sleep pattern and often feels lethargic and worn out. He has had anxiety since he was in year 4 relating to having pku and has had involvement from CAHMS, SIPS, and the health phycology team.
In school and at home when his blood phe levels are raised he becomes easily irritated, has low moods and this has often been referred to as ADHD type behaviour. He has had troubles with being paranoid and afraid of things such as the dark, walking alone, and has been over sensitive to scary stories or films. He has only ever shown signs of these behaviours when he has had raised phe levels.
His anxieties tend to shift to one pku related problem to another. During the lockdown he developed a fear of having his blood taken so we had to attend extra clinics at the rvi hospital so his paediatrician could take his blood with the aid of gas and air. With the help of weekly treatment from the health phycologist, this anxiety passed but has now once again shifted back onto food anxiety.
He suffered for years with aggressive mouth ulcers that is common in pku patients, this was an extremely hard period of time for us as his mouth was so sore that it was hard for him to take his protein substitute and eat enough calories for his blood phe levels to be within the recommended range. All of these associated side effects and related illnesses linked to pku DO NOT stop just because you turn 18. They are something that will be with the pku patient for life as well as the any other associated illnesses such as Neurological problems, poor mental health and cognitive depletion.

Q8. Our sons struggles are all based on the restrictiveness of his condition, the associated symptoms of pku, how it makes him feel and the implications it has on his ability to do the same activities as any other healthy child of his age. The cost of the treatments he has taken part in such as anxiety courses with SIPS, health phycology meetings, extra support, meetings and phone calls from his metabolic team are above and beyond the support given to a stable healthy child. If there is little evidence why is this? Kuvan has been Widley used in 17 other countries for the past 12 years and England is meant to be a pioneering country for medication and treatments but yet the pku community have been left miles behind.
I strongly believe that the struggles he has faced with his diet and medication, raised and lowered phenylalanine levels and the constant battles we have face with lack of knowledge or understanding of his condition have led to him not reaching his actual full academic potential. Its only because of the recent pandemic and the support from his paediatrician that his school is starting to listen and understand that with the correct support in place he can achieve his expectations. This support again is going to come at a cost!!

Q9. NICE need to take into consideration the protected characteristics when considering fair access to every treatment and the treatment of pku should be no different. . People with learning disabilities are at a higher risk of being unable to control their phenylalanine levels with dietary treatment. The need for help with dietary treatment might also restrict the independence of people with learning difficulties. To not consider the protected characteristics of individuals when making decisions is discriminatory practice. The fact that pku treatments are widely available with great success and hugely improved quality of living in other countries but not in a country that states it is a leader in medical practice is something that seriously needs to be addressed. NICE needs to take into consideration the costs that incur to the NHS from pku patients that find it impossible to adhere to the very restrictive diet and because of this suffer side effects as a result and need interaction from medical services or other forms of medication. Having access to a medication that can give a sense or normality, would enable the prevention for the need of other mental heath services, medications, higher quantity of prescription foods and excess metabolic appointments.

Q10. This is diabolical! There is plenty of evidence to show that the effects of high phe levels during pregnancy pose a greater risk of complications to the unborn. The maternal phenylketonuria (PKU) syndrome refers to the teratogenic effects of PKU during pregnancy. These effects include

mental retardation, microcephaly, congenital heart disease, and intrauterine growth retardation.
Author: Harvey L. Levy, Manijeh Ghavami
Woman with classical pku, before and during pregnancy must maintain a restrict diet and a phe level of under 300. The pressures and worries of any pregnant woman are serious enough without then having the added concerns and severe restrictions a pku woman must adhere to in order for them to give their unborn child the chance of healthy growth. When deciding that Kuvan is not cost effective in adults, NICE has ignored the benefits to women of using Kuvan to help women with PKU have safe and happy pregnancies. NICE has contradicted this decision by then stating they recognised that controlling phe levels is important in early pregnancy, ideally before conception, and has recognised that this would reduce the risks of Maternal PKU syndrome. However the harms from high levels in early pregnancy have not been included in their cost analysis. I strongly believe that NICE has failed to take account of the issues experienced by women with PKU and that this is a major failing in their draft guidance.

Q11. I suggest that nice speak to the pku metabolic specialists and listen to the voices of pku woman who can tell them of their fears and experiences of unexpected pregnancies or fears of falling pregnant and the impact this has had on them being able to form healthy relationships. 'Babies born to mothers with PKU who have high levels of Phe (women who are not on the special diet or do not take their medical food appropriately) are at a higher chance of being born smaller, having microcephaly (baby's head is much smaller than expected), intellectual disability, behaviour problems, heart defects, and seizures.' It is ludacris that nice have suggested there is no evidence to support the effects on woman with pku when I found this information with a simple search engine search.

Q12. The pku diet is an arduous one to adhere to for anyone. When there is an added risk to woman and the potential damage not adhering to the diet can have on their unborn child the stress and worries are increased and the damage to the children born can be devastating. NICE have not taken any of this into consideration. The potential risk to the child born could have a costly effect that far outweighs the cost of the prevention.

Q13. Although I understand that an average dose of 10mg/kg is appropriate for the cost analysis, I believe that clinicians should be able to prescribe within the marketing authorisation, which ranges from 5mg/kg to 20mg/kg. I do not think that there should be limitations on the amount of dose prescribed as I think that it would be unfair to assume that individuals that don't respond to 10mg wouldn't then respond to 20mg. I believe that it is ethically correct to give every child with pku a fair chance at being responsive to the drug and in order to do this the clinicians should be able to prescribe a dose of 20mg if needed.
NICE need to listen to the voices of the people who live with pku daily and not rely on poor ill-informed outdated research. More money needs to be put into understanding rare diseases and those who suffer need to be understood and not discriminated against because of the lack of knowledge and understanding.
Our son would be ecstatic if he responded to kuvan and it would diminish his anxieties and how he felt about his condition. It would open up more opportunities of social and emotional development and strengthen our family bond. It would ease the pressures I have as his carer and enable me to peruse my own career progressions.
However, my biggest concern with the proposed guidelines is that NICE have not taken into consideration the devastating effects that taking away kuvan at the age of 18 would have on any individual. I know of no other medication that is taken away at the age of 18, and I think to do that to an individual with pku after they have been enabled to follow a less restrictive diet (all thanks to kuvan), and then expected to stop eating the foods they have become accustomed to because now they have to follow a limited protein diet is both unsustainable, cruel and unethical. I would like to request that NICE also take into consideration that biomarin will soon loose the patent for kuvan, making way for cheaper versions of the drug to be produced and that the cost effectiveness of this treatment will far out way the additional treatments that many pku patients access at the moment.I hope that NICE reconsider their proposed guidelines and have compassion when reviewing their decision. I hope they now have a better understanding of the daily struggles pku brings to individuals and their families.

Respondent 65

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. It would prove incredibly difficult to reduce my daughters exchanges once she turned 18 , routine , habit and personal tastes and dislikes would be embedded by then not to mention the brain fog she wound experience with reducing down her natural protein once again

Q3. I do not agree with NICE's view

Q4. My daughter has always had levels within the recommended range but suffers from poor concentration and speech issues all of this has improved since we paid privately for Kuvan I firmly believe brain damage would be caused by stopping her Kuvan at age 18

Q5. Absolutely agree - making separate dishes and shopping for such a restricted diet is incredibly hard. It affects being able to go abroad or even go to a special family dinner . The psychological affect on all members of the family but particularly the child with Pku is underestimated

Q6. They should have taken into account the amount of time given to this condition by families . Taking blood, ordering foods and supplements, looking for foods child can eat, looking for recipes and cooking meals in advance to help with waste and time . Time organising trips to military precision getting meds ordered and foods . Other children in the family being overlooked as supplements are administered which In some cases can be difficult

Q7. Agree, my daughter has experienced all the above symptoms and these have improved on Kuvan paid for privately

Q8. My daughter was so desperately sad about feeling so different and also unable to think clearly . She has now got an.EHCP at school with massive school resources now directed at her - this cost may have been avoided with early Kuvan

Q9. *[no response given to this question]*

Q10. Recommend it for maternal Pku , pregnancy can be challenging enough without adding this also especially when nutrition is so important

Q11. No

Q12. Not all women will be in a good stable situation to manage their Pku effectively in pregnancy therefore all should be done to protect the unborn child - .

Q13. Withdrawing Kuvan at age 18 would be unethical and morally wrong these children deserve to be able to do well at university and their working and personal life - this needs to be extended to all adults . The amount of money spent on other therapies in the NHS fir therapies to fix lifestyle choices when these children have an inherited genetic disease is wrong - it is a rare disease and it deserves having current up to date treatment

Respondent 66

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Our concerns are around an abrupt stop - which at any age would be disruptive and challenging given that skills of managing at a low exchange level would likely be lost if a child has grown used to a less restrictive diet. If however this abrupt stop takes place at 18, which for many children will be during thier A-level year or immediately prior to leaving home, it will likely negatively impact both academic attainment (and hence longer term earning potential) and an ability to effectively manage thier diet at a time when they have started to leave home and prepare for an independant life. This 'double whammy' will likely increase the demand on the NHS at that time, as well as restricting employability and therefore potentially increasing the demand on the public purse.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. Whilst many adults with PKU may experience 'fogginess' or degraded mental performance as a temporary matter, putting this as a 'default position' induced by a significant change to treatment regimen will mean that de-facto mental health performance is degraded. This seems only semantically different from long term brain damage as it has the effect of restricting mental faculty over a prolonged period.

When our child was first diagnosed we were advised that this would be a diet 'for life' and that mental degredation would result if it were not adhered to across our child's life.

Q5. It is certainly the case that with a higher permissable level of protein in diet, the level of required adjustment to normal life will decrease. There are however ongoing dangers from aspartame etc. which will require continued vigilence on a 24/7 basis.

We have noted that when those coming into contact with someone with PKU notice that the rules 'seem to be selectively applied' then it can be tempting to apply a less strict approach. This is in our opinion an incorrect response; rather the level of strictness will continue, but the positive impact is that a change to increase protein allowance will change focus from "you can't do that" to "here is how you can do this". Such a change is a significant positive change to mental approach for both patient and carer.

It should also be noted that not all PKU sufferers will benefit from Kuvan (Sapropterin). As such the impact of not responding should be considered, particularly for multiple individuals within one family. Support in terms of diet management and mental health (both of patient and carers) should in our opinion be provided as part of the assessment as to whether Kuvan is clinically appropriate for a specific patient.

Q6. Some family members, particularly those for whom PKU is a less frequently encountered item, can struggle to understand and make reasonable adjustments to allow a normal social relationship to grow. This has impacted us in that some family members find it harder to cope with the needs of someone with PKU than they do other family members.

It should be noted that those diagnosed with PKU are not the only sufferers of this condition. Those having a family relationship which is affected by PKU, including (but not limited to) carers also suffer an impact to their quality of life. This might be from impact of reasonable adjustments to plans, or to curtailing a trip because there is no facility for a family member to eat a meal that is within their diet. This impacts the quality of their life, social opportunities, employment opportinities, mental health, and should in our view be a factor within Quality Adjusted Life Years assessments. It should also be noted that this may impact in terms of flexibility required from employers, which impacts the potential employment routes for carers, retention in employment role and resultant stress and financial impact both to the carer and the wider economy.

It should be noted that schools often find that EHC plan processes do not rate PKU sufficiently to prioritise PKU suffers for EHCP assessment, or funding for reasonable adjustments. This can mean that increased carer input is required to the school environment and also increased Teacher and Teaching Assessment time is required to ensure equitable treatment for both those with PKU in a class and the rest of the cohort.

Q7. Whilst we support the committee's conclusion, we would add to the list insatiability of appetite within the diet resulting in a prolonged feeling of hunger, which can negatively impact the mental health of both patient and carer.

Q8. Metabolic clinics are located in centres of excellence. Therefore an estimate could reasonably be made as to the normal travel length and cost(noting this can be quite lengthy in rural areas), the cost of this time both to the patient (including education time lost), parents and carer time off work, and of the impact to the NHS in having such clinic time used up.

Schools can find it challenging to release extra funding through the EHCP process, and as such existing school budgets are put under pressure to deliver the needs of those with PKU, which negatively impacts the provision for all children.

NICE could also consider the impact on family units, ultimately culminating in a divorce or breakdown of the family. This can cause costs to the public purse and negatively impact mental health and development of the PKU sufferer and their family (including those not living at the family home). A discussion covering some indicative costs associated with such breakdown for the welfare budget was held in the House of Lords on 4th March 2014 (https://www.theyworkforyou.com/lords/?id=2014-03-04a.1214.8) and, whilst these figures would need to be adjusted to be current, they provide a quantitative basis for costing this impact.
Such relationship breakdown is known to have a negative impact on the mental health of teenagers (https://ifstudies.org/blog/the-link-between-family-breakdown-and-teen-mental-health-problems-in-the-uk) and it cannot be forgotten that these are the very people that a cessation of provision at age 18 would impact, and likely for whom make mental processing harder.

Moreover, the figures I would be considering are the opportunity cost of PKU. By this I mean that those able to keep to diet, especially when strict, often self-limit life opportunities due to the diet. The costs for society in not getting the best from the potential of all of its members is clearly unmeasurable, however it should be noted that with an effective treatment, PKU should not significantly impact mental development. Kuvan (sapropterin) would increase the pool of those who are able to adhere to diet and as such achieve thier potential.

Q9. It should be a point of ethical debate whether it is reasonable to withdraw on a cliff edge (or in a gradual way) a treatment from people who have reached a particular age not on health grounds (the clinical efficacy is not being debated here) but rather on cost grounds.

It is perhaps a different factor for those who already are in Adulthood without Kuvan (sapropterin) to manage as opposed to those currently children who would become adults without the finely honed skills and techniques which parents and carers seek to instil to manage a tightly controlled diet.

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. It should not be underestimated that the prescription cost of such diet items for adults will continue to impact the taxpayer; pre-payment will limit the cost to the individual of such prescriptions and the taxpayer will pick up the cost for the rest. As such, any relaxation of diet and hence minimisation of the cost of medically processed foods should be factored into the cost to provision of Kuvan to adults.

On the subject of children; Parents who have PKU and have not achieved high compliance with diet may struggle to manage children effectively whether or not the child is a PKU sufferer themselves. As such it should be considered whether parents who have PKU (or those with PKU considering becoming parents) should also be eligable for access to Kuvan to help control diet.

Whilst we support the recommendation to approve Kuvan (sapropterin) treatment, we feel that without a wider availability it will cause many carers to have to make an ethical judgement as to whether it is fair to offer something that has a high emotional appeal but may not work for the individual, knowing there is a very limited period over which this will be available (i.e. until the age of 18).
Therefore we would urge NICE to approve not only in childhood but also for adults of working age (and older).

Respondent 67

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. 18 year old that have been accustomed to a relaxed diet from using Kuvan will find it extremely difficult to switch to a strick dietary regime They will not have coping skills.
Neither has the effects on pregnancy been considered,neither has the effects on adults with learning disabilities .

Q3. NICE's statements are contradictory

Q4. research conducted by NSPKU recognises that many adults with PKU have serious brain damage symptoms caused by high levels of phenylalanine .

Q5. I agree absolutely .The strain on families and carers must be tremendous .Having to be so accurate forever takes its toll financially and socially .

Q6. Yes the effects on other family members can be far reaching with a social and economic cost to the community far more than the cost of making Kuvan available for all people with PKU.

Q7. Our granddaughter struggles with focus at school and has started to feel marginalised by the effects her supplement has on her as in bowel movement being erratic .It can be hard enough being small and at school but when you are made to feel so different it can feel like torture .No child should have to go through this when the right medication will negate the effects of PKU.

Q8. NICE needs to gather the will to ensure that information is gathered on long term brain damage because of PKU.Consultation with NSPKU would go a long way to put this right

Q9. NICE has not considered treating people fairly.Even discounting the social cost the additional cost to the NHS treating people who have become ill physically and or mentally due to PKU will far outweigh the cost of funding Kuvan for all.

Q10. NICE should recommend the use of Kuvan for pregnant women so as to control the levels of phe in pregnancy .

Q11. NICE has recognised the importance of controlling phe levels in women in early pregnancy so surely it would make sense thatpregnant women with PKU should given Kuvan.

Q12. This is a terrible oversight.The social and economic costs will far outweigh any costs attributed to the supply of Kuvan

Q13. NICE have been far too conservative in their estimation of 10 mg max of Kuvan when evidence from NSPKU shows that most people respond between 10 and 20 mg.
A lower dose will be ineffective and therefore not cost effective .

Respondent 68

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I believe that living a life with being able to sample more protein intake and then taking it away at the age of 18 would be damaging and detrimental to health, mental health and wellbeing! Its damaging.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. I dont have any experience of long term brain damage in adults, I would like some more evidence to be able to comment.

Q5. I completely agree with this. I myself have had to give up a full time job to be able to manage my sons diet. I would welcome any support to help my son live a more normal life. Its a huge strain on his daily life. He sits and watches people three times a day eat what he would long to!

Q6. The value to us as a family is like winning the lottery! I would give up everything to have this for my son. The strain it has on his siblings/ grandparents and parents is unbelievable. Imagine the guilt each time you sit in front of a child and eat what he cant. For any one of us to be able to say ‘yes’ you can have that instead of ‘no sorry, your not allowed that’ every time my child asks for something!

Q7. My son suffers with all of these symptoms daily. I completely agree with this statement.

Q8. My son needs support however he only gets support from his family. He has been referred but due to current council and costs ect he is left alone to fend for himself.

Q9. I understand that its costly for me to treat my son due to the foods i give him, fresh fruit and veg daily and some vegan/low pro and fresh low pro shop bought yogurt, that can be shop bought is very expensive. So this could be tricky for low income families.

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. I believe that more than 10 mg may be needed for individuals whom will respond and if needed should get it. I also believe that taking this drug away from an 18 year old is unbelievable. And should not even be up for discussion. I welcome the drug for my son and this is amazing news. Thank you but please re consider the long term in adults too!

Respondent 69

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I do not agree with stopping kuvan at age 18 managing diet in teenage years as this is a life long condition I ask you are saying “ at age 18 they are cured “ have you considered at this age they could be considering a family of their own and the strict diet they would need to,follow to avoid their unborn child having brain damage or possibly physical and mental disabilities.

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. I,do,agree that carers and parents would welcome a less strict diet. I have seen my grandaughter hide in a toy box a cupboard cry her heart out as the special tummy milk is absolutely foul tasting believe me I tasted it, I’ve seen her wretching as she tries to drink it. I’ve watched her mum breaking her heart as she knows ******** must have this medicine. I’ve also seen ******** upset because there was a birthday party at school and she could,not have a piece of birthday cake and her teachers had forgot to inform her mum. Imagine the stress and total heartbreak for a little girl. Why am I different mummy. It’s completely wrong

Q6. Yea they,should,consider the impact of this on all family members. Grandparents cannot just help with childminding due to the strict diet the sufferer must follow. The sufferer cannot enjoy the same pleasures of,going for a sleep over with her friends, I personally cannot take my grandchild for a holiday a weekend break in case her levels rise and she needs more support or medication

Q7. As previously mentioned the emotional strain on ******** has been disturbing, she does have concentration problems and finds things difficult at times this in turn puts her parents in turmoil with unnecessary stress when there is medicine that can help with this condition

Q8. My grandaughter attends a private school due to the fact stream line education schools are heavily populated and they could not cope with her diet requirements. This took the decision of having second child away from her parents as they simply could not afford to give a second the child the same private education. They have sold their holiday home to afford ******** education, also ******** struggles in certain areas of her education and needs the extra attention her teachers can give her. Finding products with no protein content is virtually impossible and are usually expensive another strain on family income there are a lot of grandchildren in our family who can have normal food and sweeties whereas ******** cannot have the same and finding the correct content for her is not only expensive but very stressful and yet another strain on family and parents and obviously yet again making ******** extremely unhappy as in her words “why am I different”

Q9. Absolutely not. People from all walks of life with pku need this medicine, by not providing it to all sufferers it’s a form of discrimination and stopping it at the age of 18 is absolutely appalling.

Q10. Not to stop kuvan at the age of 18 why would they do that, they are committing these young adults to a life sentence and the choice of do I become a mother or not what right have they got when they hold the medicine in their hands to give them the chance of a normal life including a family of their own.

Q11. It’s an absolute must to help avoid the chance of any abnormalities in the unborn child . Have any if these people lived with a pku sufferer do they know how hard it is.

Q12. The cost of kuvan is far less than the cost on The NHS treating the side effects of pku sufferers in particular uncontrolled pku in mothers this could result in high child care and even foster care costs and immeasuarbale long term damage to,the child

Q13. The cap of 10mg needs to be removed you cannot measure the health wellbeing and quality of life in pound notes. Give each and every pku individual sufferer what they need to help them lead a normal and stress free life enjoying the things we take for granted. When al is said and

done these children teenagers young adults did not ask to be born with this illness, and their parents would lay life and limb down to take it away from them. Give them the medication they require REMOVE THE 10MG CAP

Respondent 70

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. It is totally unfair to give children medication which helps to live life fuller and to experience new diets, changes, and experiences. Totally unjustified to withdraw this help just because of a number. It is everyone’s human rights to have help to live a full life.

Q3. I do not agree with NICE's view

Q4. I have been a support worker for MENCAP. During this time I have supported people with learning difficulties which has arisen from long term brain damage. If there is any chance to stop brain damage or anyway of holding back long term brain damage. There you have a duty to do so.

Q5. Yes I totally agree with this statement. I have a grandson with PKU. The effects on the family, especially the prime carer, the mother is very upsetting for myself to witness. The family feel lots of pressure to keep the diet to a minimum. Having to check items of food. Having to say NO. To change the diet so it is delicious. To go grocery shopping and take hours to read packages on the protein included. Also the stress of relationships within the family. I myself as a grandmother find it difficult as all the meals have to be weighed and protein counted. Surely, if there is help available wouldn’t it be the correct and rightful duty to give this medication.

Q6. Yes. NICE should take into account the full family unit. As the effect is felt throughout the family. Brothers, sisters, aunts, uncles, ECT. This is stress which bounces from one family member to another.

Q7. Agree most definitely. The well being of a person and family unit must come first.

Q8. Why are people with PKU treated as second class citizens? The answer is because PKU is so rare that the goverment do not want to spend money on a small quantity of the population. So unfair. These children/adults did not ask for this appalling condition.

Q9. Everyone deserves to be treated fairly. Not matter what their colour, gender, sex or disability.I feel we need to fight to action this.

Q10. Testing throughout pregnancy when one parents is know to have PKU

Q11. No evidence but studies needed.

Q12. Costs should be given for tests

Q13. I am willing to fight for my grandson and other people to have a normal life. Free from the stress of food and being ruled in the everyday life by protein. Free these people. NICE have the power to do this.

Respondent 71

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. You cannot give then take away. This is cruel.

Q3. I do not agree with NICE's view

Q4. I have witness my family under great stress and anxiety due to the fact that I have a grandson with PKU.

Q5. My daughter can only work part time due to my grandsons pku. There is an extra room which houses his medication and foods. His prescription foods have to be ordered and delivered at a time which is usually inconvenient. This takes up extra days in the month.

Q6. Yes all family members will benefit from Kuvan.

Q7. Yes. I have definitely noticed the impact of the PKU diet. Which has ALL the above symptoms.

Q8. Not enough evidence collected. This needs to be changed.

Q9. Not treated fairly at all. It seems that all is connected to money and expenses. Surely a right to a normal life is what is expected from NICE.

Q10. More data required so as to make a decision. Therefore more money needs to be allowed to help gather information.

Q11. Sort more help.

Q12. NICE need to calculate costs to prevent babies being born with PKU then hopefully it can be irradiated.

Q13. I am hopeful that the right decision is made regarding giving Kuvan to over 18/adults. People do not stop being a PKU victim at the magical age of 18!!! Very angry.

Respondent 72

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. It is highly unethical to allow treatment of PKU and those that suffer to become accustomed to a more flexible diet and then have this removed on their 18th Birthday. In my opinion this will place many at risk of on going emotional issues and directly impact on their daily lives.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. As a mother of a young child with PKU I can confirm that my experience includes all of the above. Supporting my daughter around her PKU can at times be very stressful and I constantly worry for her future, already at such a young age she needs to be treated differently from that of her peers and no doubt will soon pick up on this fact. I'm sure there will come a time where she will want to rebel against her tough restrictions on her diet in order to fit in with society norms, this is an extremely worrying concept as her parent as I understand the impacts this can have on her development, emotional health and lasting effects on her adult life.

Q6. Yes.

Q7. Yes I agree.

Q8. My daughter is only 3 years old however I already witness the additional costs placed upon health and other services associated with her condition, this includes the ordering and delivery of frequent prescriptions, one to one supervision at nursery / education, staff training by the metabolic team, more frequent visits to the GP due to the worry that when she is unwell this will raise her levels. I suspect as she grows older the associated costs will increase without appropriate treatment being available.

Q9. *[no response given to this question]*

Q10. I believe that every effort should be made to make treatment available which could improve the health chances for a mother and baby, costs around this should not be a factor.

Q11. As above

Q12. Costs should not be a factor in supporting the health of a newborn baby when there are preventative measures clearly available on the market

Q13. We all want the best for our children, as a parent hearing the news that your baby has any health condition is heartbreaking. When there is a known treatment that could potentially improve the quality of life for an individual this should be available to them throughout their entire lives. Withholding this and potentially discriminating treatment dependant on age is highly unethical and immoral. Kuvan should be available to all who may respond to the treatment.

Respondent 73

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. If the proposal goes ahead my grandson will have lived half of his life with the benefits of KUVAN at a time when he is transitioning into independence and adulthood. I know from my experience with my own son, who has not got any additional needs this was a very challenging time.

Young adults have so many changes and challenges that the majority place no priority on the food they eat, preferring to grab takeaways and easy to prepare processed foods.

There would seem to be no consideration of the difficulties stopping at 18 would bring the only factor considered is the cost. There are fundamental concerns that his would be profoundly damaging to a young adult. The affect on their ability to maintain studies/jobs, ability to manage social interactions will be impacted negatively.

It is unethical to remove standard foods such as bread, pulses - basic foods for most people that will allow someone with PKU to eat a more "normal" diet which is much easier to organise both at home but also and much more importantly at this age when out in social situations.

Q3. I do not agree with NICE's view

Q4. I have spoken to and have friends via the NSPKU and the PKU community that are adults who were advised to stop the diet. Examples of the types of issues they face are
*depression
*inability to focus
*headaches
*cognitive executive function impairment
* brain fog
* low energy
*neurological pains in the body
*general ability to cope
*anxiety
*difficulty understanding instructions
*poor memory
*lack of concentration

The ability to hold down a job, manage your own affairs and home, complete studies would be massively impacted by the above and the expectations that young adults will manage on diet alone is naïve at best. There is a wealth of evidence that demonstrates that adults struggle to maintain recommended levels even when on diet as the diet is so difficult to maintain

Q5. Absolutely, as a grandmother I actually left work to support my son and his wife so they could both work without worrying about additional care for the children, one of the main reasons for this is because of my grandsons PKU.

Constantly trying to balance everyone's food so that meals are similar means meals take longer to plan, shop for and prepare.

School has a Health plan in place but on any discussion with a teacher the response is oh it's like gluten free isn't it?

Waiting for the results of a blood spot knowing that might mean a change in exchanges and therefor planned meals for the week is at best frustrating. Most families can plan a meal and not worry, a change in levels can mean the whole weeks food changes not just one meal but 3 meals a day and any snacks.

Q6. Yes of course the affect of treatment is holistic and affects so many within the family. As mentioned above I left work, I was fortunate enough to be able to afford to do so but that has of course had a massive impact on our income levels and we are more financially restricted than ever before.

Q7. I do agree with a few of the difficulties and these are when levels are elevated rather than high. My grandson is on diet and has higher levels, sometimes because he has sneaked something extra which is something children do.

Do NICE think these symptoms disappear at 18? The evidence from PKU sufferers demonstrates this is not the case, they do not stop at 25, they do not stop at 40, PKU is a lifelong condition!

Q8. He has had additional support which I have no idea regarding the costs although I imagine they are significant

Q9. There is a basic lack of equality in the cut off of 18, people with PKU face sensory and cognitive impairment from elevated levels regardless of their gender or social/economic status. PHE attacks the brain regardless of age and causes issues that impact all people of all ages differently.

A decision based only on cost is completely unethical, KUVAN will not be suitable for everyone but everyone it is suitable for should be able to access this, diet is not a treatment it was for many years the only way to manage the conditions and make sure that suffers had as little detrimental effect as possible.

Treatments have moved on and there are treatments that can provide sufferers with the ability to maintain levels within a fairly normal diet.

Q10. I think KUVAN should be offered to all suffers who respond including pregnant women.

Q11. I have no direct knowledge

Q12. I have no direct knowledge

Q13. The ability for people with PKU to eat a more normal diet is not the primary reason for me supporting KUVAN for all, it is the associated impact of this.

The mental health benefits of having well maintained levels with help with social relationships, the ability to function well at work and progress within ones chosen field. These are not big expectations they are the things that the majority of people take for granted but is not the norm within the PKU community.

Respondent 74

Q1. For Children and Adults with pku, but especially under 18s

Q2. *[no response given to this question]*

Q3. I do not agree with NICE's view;As a patient with pku I know the positive effects of Kuvan as an adult and how it helped my cognitive abilities and led me to be able to think and concentrate much much easier

Q4. As an adult patient fortunate enough to receive kuvan I can compare my cognitive abilities before and during treatment. Receiving Kuvan as a triallist in the early days and fortunate enough to receive the drug I noticed I could concentrate, and do simple tasks easier such a sitting still, reading & writing. Following the Kuvan trial at age 29 I felt I had the confidence to go to university and study a career in nursing. Something I never thought I would do due to not being able to concentrate while on diet and supplements. At now 39 I am now a charge nurse in a busy paediatric emergency department and life on Kuvan is so much better and quality of life is also so much more positive for me and my family. Although I may not have long term brain damage there have been detrimental effects on my cognitive abilities.

Q5. I agree with this. Quality of life becomes easier not just for the PKU patient but the family as a whole as well. Even just going out for the day is a more positive experience. And although there are a lot of low protein food products now, they are not all the most pleasant to eat. This can cause stress for a family, and have a negative effects on mental health for all.

Q6. Yes

Q7. I agree with this.

Q8. Any of the effects of living with high Phe levels should be taken into account as a financial cost to a patients care.

Q9. I agree that children should be prioritised for kuvan as they are growing and developing and vulnerable to high blood Phe levels. However Adults who are continuously trying to control their levels using diet and supplements should be considered especially if Phe remains high and is effecting them negatively. Cost should be taken into account for their counselling and mental health

Q10. Women should be prioritised for Kuvan when conceiving and in pregnancy. Due to the complexities of managing diet and risks to the foetus.

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 75

Q1. Whilst I welcome the decision to fund Kuvan for children under the age of 18 I am shocked and worried that NICE have come to this decision. This is a dangerous and unethical decision that will have long term implications beyond comprehension. It also shows a complete lack of understanding of PKU.

Q2. To remove treatment from a person with PKU is both unethical and dangerous. I have a number of concerns relating to this decision which I can base on our own experience. My son is 14 and has classic PKU. He has been taking Kuvan for 3 years. We pay privately for less than half a dose. This has more than doubled his exchanges from 8 to 17/18 g of protein per day. This has allowed my son to relax his diet in a way that we never thought possible. He can firstly eats foods such as potatoes, rice and cereals (which previously had to be weighed) in much greater quantities. It allows him to eat a whole host of foods that would not have been possible for example 'normal' bread, vegetarian products such as sausages and burgers, pulses and beans. It also allows him to freedom to eat out. He can now enjoy a vegetarian Subway with his friends or a hot chocolate at Costa. This would not have have been possible before. It also means he has been able to drop one of the three foul tasting amino acid supplements he has to take each day. This has made such a difference to him.
The increase in exchanges has had a number of hugely positive effects on his health and wellbeing.
When reading these please consider that these benefits will be removed if Kuvan is taken away from him at 18!

1) Having suffered with extremely painful tummy issues from being a small child this was the main reason we tried Kuvan. My son missed many days of schooling due to tummy ache and diarrhoea and developed anxiety around needing to go to the toilet. Within a matter of weeks of taking Kuvan his digestive issues stopped COMPLETELY and I attribute this to the increase in natural protein in his diet that he was not getting from prescription food which largely made up his diet.
2) He also suffers from impaired cognitive function and processing. Something that is very common with PKU. His concentration was also poor. He had difficulty writing and struggled to keep up in class.This was confirmed through assessment by an educational psychologist. We have seen a huge improvement particularly in his concentration and he has managed the transition to Senior school and then onto year 10 better than I ever thought possible. I am pleased to say he is studying for 7 GCSE's. I attribute this to Kuvan I think it would have been a very different story had he not been taking it.
3)He only has to take two rather than three amino acid supplements now. These are a foul tasting but essential part of the PKU dietary regime. My son detested taking his lunch time one at school. It made him stand out in front of his peers and he was highly embarrassed as it caused his breath to smell. This supplement was dropped as a result of taking Kuvan. The anxiety a young adult experiences at being different should never be underestimated. The reduction in supplement has also reduced the issues of mouth ulcers (below) and digestive problems previously mentioned.
4)My son also suffered from frequent and persistent painful mouth ulcers. Something that is common with the PKU dietary regime. They would make him cry and prevent him from taking the harsh acid supplement that he must have. We had regular rips to the doctors but nothing worked.He has had two mouth ulcers in the three years he has been on Kuvan.
5) He has become a happier and more relaxed individual since taking Kuvan. He is much less anxious and is able to fit in with his peers.

To remove Kuvan at age 18 would essentially be removing food from him. He will have to return to a diet based on fruit some vegetables and largely prescription food. This diet is hugely difficult to manage at the best of times never mind for an 18 year old who has not been required to do this before. The removal of kuvan will mean the return to a synthetic diet and the return of health issues which plagued his childhood and undoubtedly the cognitive issues I have touched upon. All at a such a crucial time in his life when he may be studying for A levels, moving to University or starting a full time job. With it will return the anxieties around adoption of an extremely difficult and unsociable dietary regime.

In my opinion withdrawl of treatment at 18 will result in a huge number of people with PKU not be able to stick to the dietary regime and being unable to control their levels. Some peoples diet on Kuvan may well be even more relaxed than my sons and include eggs and even meat. This will be taken away!They will then start to experience the unpleasant side effects of high levels which will undoubtedly have a massively negative impact on their lives.

I would like to draw your attention to the UK strategy for rare diseases. This promises
'a seamless pathway for patients with rare diseases to transition from childhood to adolescence and on to adult and older age' it also promises 'to co ordinate care so as not to disrupt patients work or eduction'. The NICE guidance on use of kuvan and its recommendation to stop treatment at 18 flies in the face of this. I ask you to please re think this before another error is made (and there have been many) in treating this condition.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. The NICE statement is hugely contradictory. It states that brain development does not stop until age 25 but proposes removal of Kuvan at age 18. How can removal of a treatment be justified at 18 when a young adult is embarking on new and important life experiences such as doing further qualifications, university/college/ first full time job. To be faced with a strict dietary regime and the probable elevated levels that could result would be hugely detrimental.

Q5. Totally agree. The PKU condition is hugely difficult to manage.I didn't return to work as an Environmental Health Officer because of the time it involved. of the limited foods he can have foods other than fruit and a few vegetables have to be weighed and calculated. Meals must be cooked from scratch. I had to bake all of his bread and cakes etc. It is a fine balancing act ordering and managing prescriptions.
There is also a need to eductae people at every turn. PKU is not understood for a number of reasons but mainly because it is so rare so they haven't heard of it and also because it is so complicated. I have had to intervene on my occasions at school because things have 'gone wrong'. One teacher didn't clean my sons supplement pot out properly between uses. My son didn't want to say anything (he was 6) but broke down one evening and said when he took his supplement it was like drinking sick. On examination of the pot we discovered this to be true. It was stinking. There have been many mistakes in school meal provision despite countless visits and telephone calls. My son was served gammon on one occasion and on another a jelly containing aspartame (aspartame is also toxic to people with PKU). On another occasion my son had observed a school cook just putting chips on his plate without weighing them. This is just a few examples. Each year I have to talk to each new form teacher and encourage them to call me should there be any questions or issues. Whilst this has decreased since my son has got older I still have very close contact with his school kitchen. All of this is extremely stressful and causes great anxiety.
In addition as a youngster going to parties we always had to take his own food as he couldn't eat any of it. There were always questions and

whispering. My son found it very hard to deal with. As a family we didn't want to stop eating out but the number of times we did reduced more and more as he got older as the only thing he could have on many menu's was chips and salad.

Kuvan has changed life massively for us. I no longer have to bake bread and cake products anymore (at all) as he has enough exchanges to eat shop bought ones. I use a lot of vegetarian products which are plentiful on the market now such as veggie fingers, burgers and nuggets. We can eat out as a family as there is much more available on a menu as he has so many more exchanges.

Q6. Definitely. I did not return to works as previously stated (I was an environmental health officer)as the care of my son took up too much time. It is not just about the lack of food and the reliance upon prescription food although this is bad enough. There were the other issues I have previously touched upon - learning difficulties, poor health. I also suffered from anxiety surrounding my sons condition as did he. This contributed I think to my not returning to any form of employment.

Q7. As I have previously mentioned my son had a number of issues associated with PKU and my worry is that if you take Kuvan away at 18 these will return. The resolution of these issues removed a significant amount of anxiety for him and me. His life was blighted by digestive problems which have now disappeared as have the mouth ulcers. His long term outlook educationally has improved dramatically. I had considered that my son might never manage in senior school and that we would have to look for alternatives or require significant support. The fact that he manages very well with a small amount of SEN support (as do many in his year group) and is managing 7 GCSE'S very well has been a weight off my shoulders. My husband and I took the very stressful decision to fund a half dose of kuvan ourselves because we didn't want to look back with regret at what might have been and I would do it all again.

Q8. Why is there no evidence? Kuvan is used throughout Europe and the rest of the world and has been for 12 years. Why is this? Because it hugely improves quality of life and a persons outcome. Why must the UK refuse to see what everyone recognises.
Pre kuvan my son has had additional help from our hospital regarding anxiety with blood taking, significant SEN intervention at primary school, frequent trips to the doctors because of mouth ulcers and digestive problems and a number of missed days at school due to tummy problems.

Q9. People with learning difficulties, sensory impairment, cognitive impairment , autism could have their lives hugely improved with Kuvan. Many will struggle with the diet as they have additional issues surrounding foods texture issues for example. Others may rely completely on someone else to manage the diet for them.
The number of people with both diabetes and PKU must be so small. Life must be hugely challenging for these people Kuvan would improve their quality of life dramatically.
NICE have been extremely unfair in these cases.

Q10. Every woman is entitled to a safe happy and healthy pregnancy. The challenge of having a baby as a woman with PKU is so great that many women with PKU choose not to do so. Phe levels must be kept below 200 micromols/litre to ensure the baby is not born disabled. Do NICE know how difficult it is to do this? That in the year 2021 there is a treatment available that will stop a baby being born with extreme disability and it is not being used in the UK is in itself a scandal. Kuvan helps a female manage their diet so they can eat healthily without worry at a time when many are tired, have morning sickness and are anxious. Please refer to the UK strategy for rare disease which promises to 'help pregnant women to eat well '. By refusing kuvan to pregnant women you are ignoring this promise. A pregnant woman with PKU in the UK must live on a diet of little or no protein or carbohydrates. It is disgraceful.

Q11. A woman should not have to worry about getting pregnant for fear of causing extreme disability at any time whether planning pregnancy or not when there is a drug available that would ensure they are following a diet that would keep their phe at a safe level.

Q12. What cost can you place on preventing a child being born without disability. Why has this not been taken into account? the cost of caring for a child with any of the disabilities that result from a poorly managed PKU diet during pregnancy would be huge.

Q13. The experts claim that 50% of adults are on diet. 30% are not. 20% have difficulty maintaining it. I disagree with this and would like to know where they get their figures from. I believe the number of adults struggling to maintain a safe phe level is much much greater and that as a result there is a huge number of adult PKU patients that are experiencing the hugely negative side effects of raised levels. This in turn is impacting their lives in a host of ways from managing education, jobs and /or family life.
Please refer to the study 'High Phenylalanine levels directly affect mood and sustained attention in adults with PKU: a randomised double blind placebo controlled crossover trial (published in the Journal of Inherited Metabolic Disease 2010) which found that elevated phe was associated with negative effects on sustained attention as well as mood.
To not offer Kuvan to adults is discriminatory. If there is not enough evidence to justify why adults need kuvan then more research needs to be done. Diet for life was introduced in 1993 by the UK Medical Research Council for a reason. Our adults need just as much assistance in helping to follow this diet as our children.

Respondent 76

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. 18 year olds that have been accustomed to a relaxed diet will not have the coping strategy to stick to a strick regime that PKU requires.

Q3. NICE's statements are contradictory

Q4. Research conducted by NSPKU recognises that many adults with PKU have serious brain damage symptoms caused by high levels of phe.

Q5. I agree absolutely .The strain on carers and families must be tremendous.Having to be so accurate forever takes its toll financially and socially .

Q6. Yes the effects on other family members can be far reaching with a social and economic cost to the community far more than the cost of making Kuvan available to all with PKU.

Q7. Our granddaughter struggles with focus at school and has started to feel marginalised by the effects that the supplement has on her,as in her bowel movements being erratic.It can be hard enough being a child at school but when you are made to feel so different it can feel like tote torture.

Q8. NICE needs to gather the will to ensure the information is gathered on long term brain damage because of PKU.Consultatin with NSPKU would put this right.

Q9. NICE has not considered treating people fairly .Even discounting the social cost the additional cost to the NHS treating who have become physically and or mentally ill due to PKU will far outweigh the cost of funding Kuvan for all PKU sufferers .

Q10. NICE should recommend the use of Kuvan for pregnant women so as to control the levels of phe in pregnancy which will endanger the unborn child.

Q11. NICE has recognised the importance of controlling levels of phe in women in early pregnancy so surely it would make sense that pregnant women have access to Kuvan.

Q12. This is a terrible oversight .The social and economic costs will far outweigh any costs attributed to the supply of Kuvan.

Q13. NICE has been too conservative in their estimation of 10mg maximum of Kuvan when evidence from NSPKU shows that most people respond to between 10 and 20mg.
A lower dose will be ineffective and therefore not cost effective .

Respondent 77

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. This is discriminatory and dangerous. Taking children off of the diet or at least increasing exchanges dramatically and then saying at 18 they have to move back or even start for the first time the severely restricted PKU diet is morally and ethically abhorrent.

Q3. NICE's statements are contradictory

Q4. My daughter suffers with problems of brain fog, anxiety, concentration and other mood issues when her levels are unstable. There are many adults who have abnormal MRI's with PKU, and the brain in fact, does not reach maturity until at least 25 but more like 30 with new brain cells produced even in old age. Thus damage to the brain can be life long with PKU.

Q5. PKU has caused food to be a medicine in my house. We have policed ever mouthful my daughter has eaten, although now she is an adult at University this is more difficult, I still am studying what she is eating and supporting her diet, ordering foods which come from three different chemists/manufaturers, preparing food, shopping with her which is 3 times more expensive than my normal shop, checking every label - the ingredients to commonly bought food/drinks can change and one can never assume from one week to the next that aspartame has not been included all of a sudden, especially with the sugar tax, which has caused all sorts of extra issues. My daughter has eating disorders caused by the constant attention to her food and the severe restrictions. This has been very distressing for her. Had she had access to Kuvan through her adolescent years this severe restriction could have been eased. As a result she still has mental health issues probably for life, that she needn't have had. Hanging over our heads as parents is the knowledge that all her life we have been responsible for her brain health, this is a massive burden and still continues. I have either worked part time or been self employed as the time it takes to deliver the therapy of the PKU diet is immense. If **** had Kuvan (we were told she would almost certainly be a responder after she took the genetic test years ago) she could pop to the student uni shop and buy a sandwich. She could have some toast in the morning or a proper bowl of porridge (she is only allowed just under half a normal serving of oats). She could participate fully eating out in a restaurant by being able to choose something off of the menu which is vegan. At the moment she cannot do this, as most vegan food has pulses or some kind of protein substitute. She may even have enough exchanges for fish or real cheese, which she would love to try. Food is ****'s medication.

Q6. We do not have many food items in our house as **** can struggle to stick to her diet. My other daughter non PKU has grown up all of her life without normal treats that others might have such as biscuits and crisps and chocolate in order to keep her sister safe. We all have tension where food is involved, it is rarely a pleasure for us.

Q7. With higher levels, my daughter has trouble concentrating, which is not ideal during her degree. She has both bulimia and anorexia and also diagnosed with anxiety relating to food. She can get very upset and often has daytime naps and headaches. With Kuvan her fluctuating daytime/nightime levels would be controlled.

Q8. **** has had help from the Psychology team at GOSH and also many session at the Psychtherapist team for Eating Disorders Northwick Park, for her eating disorders and for self-harm. This has cost the NHS money and would have been unnecessary if she had had the additional support of Kuvan. **** has been excluded all of her life from celebrations involving food and has had non-pku food crumbled into her food by other girls at senior school and also taunted in primary school on birthdays when she was not allowed the cakes they would share in class (despite me providing alternative permitted pku food for such moments - teachers would forget to give them to ****.) In the end **** had to change school as a result of such bullying. She was even forced to eat a non-pku meal by the dinner ladies at Christmas despite pleading with them about her PKU. She had to eat a bean burger despite me going in to full detail about what she could have on her plate on this one off special dinner. ****'s medical condition was well-known, but these sorts of mishaps happen. She would not have been so affected had she had Kuvan making mistakes like these less dangerous.

Q9. **** is terrified of getting pregnant and has even discussed not having a child as she doesn't know how she could cope with 0 exchanges. Furthermore she has suspected endometriosis and has diagnosed polycystic ovaries. For her getting pregnant could take many years, which would mean for her many years on around 0 exchanges in order to keep any potential child's brain safe. This is totally unacceptable and particularly discriminatory, not to mention dangerous for the child and mother.

Q10. Women of child bearing age must have Kuvan. Pregnancy without controlled levels is unfair to the child who through no fault of the mother or child could be born severely disabled. This is totally immoral and unethical.

Q11. **** could take many years to get pregnant. It's safe to say a percentage of women with PKU will take a long time to get pregnant. The PKU diet is severe when planning a pregnancy this would be intolerable for any length of time, but probably impossible for someone like ****. Sh e should not be denied the chance of becoming a mother due to this discriminatory decision.

Q12. I agree NICE's calculations do not include these costs and also do not include a projection of potential social care problems in elderly PKU patients, who will need extra support in homes, probably one on one care to delivery the PKU diet therapy and also has not included dementia risk, cost calculations.

Q13. It was shocking to see the decision. It is discrimination and totally unethical to suggest stopping this treatment at 18. How could NICE even consider for instance a 16 year old on Kuvan for 2 years tasting the freedom of a normal diet and then putting them through the trauma of trying to follow the severe regime that is the pKU diet. They will be set up for failure, mental illness, and horrible side effects from not being able to cope with such a change. For adults who have waited and campaigned like **** most of their lives for this drug it is the ultimate insult to be barred from it. No other drug is taken off of someone when they reach adulthood. It's disgusting and I am appalled. Clearly the evidence provided by PKU sufferers has been ignored. Evidence regarding the effects on the brain in adults has been ignored. We know white matter damage occurs in PKU patients, it's documented and has been presented to NICE why has this been ignored.

Respondent 78

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. If the proposal goes ahead my grandson will have lived half of his life with the benefits of KUVAN at a time when he is transitioning into independence and adulthood. I know from my experience with my own son, who has not got any additional needs this was a very challenging time.

Young adults have so many changes and challenges that the majority place no priority on the food they eat, preferring to grab takeaways and easy to prepare processed foods.

There would seem to be no consideration of the difficulties stopping at 18 would bring the only factor considered is the cost. There are fundamental concerns that his would be profoundly damaging to a young adult. The affect on their ability to maintain studies/jobs, ability to manage social interactions will be impacted negatively.

It is unethical to remove standard foods such as bread, pulses - basic foods for most people that will allow someone with PKU to eat a more "normal" diet which is much easier to organise both at home but also and much more importantly at this age when out in social situations.

Q3. I do not agree with NICE's view

Q4. . I have spoken to and have friends via the NSPKU and the PKU community that are adults who were advised to stop the diet. Examples of the types of issues they face are
*depression
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*headaches
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The ability to hold down a job, manage your own affairs and home, complete studies would be massively impacted by the above and the expectations that young adults will manage on diet alone is naïve at best. There is a wealth of evidence that demonstrates that adults struggle to maintain recommended levels even when on diet as the diet is so difficult to maintain

Q5. Absolutely, as a grandfather I actually reduced my work hours to support my son and his wife and to support my wife, so they could both work without worrying about additional care for the children, one of the main reasons for this is because of my grandsons PKU.

Constantly trying to balance everyone's food so that meals are similar means meals take longer to plan, shop for and prepare.

School has a Health plan in place but on any discussion with a teacher the response is oh it's like gluten free isn't it?

Waiting for the results of a blood spot knowing that might mean a change in exchanges and therefor planned meals for the week is at best frustrating. Most families can plan a meal and not worry, a change in levels can mean the whole weeks food changes not just one meal but 3 meals a day and any snacks.

Q6. Yes of course the affect of treatment is holistic and affects so many within the family. As mentioned above I reduced my hours of work, I was fortunate enough to be able to afford to do so but that has of course had a massive impact on our income levels and we are more financially restricted than ever before.

Q7. . I do agree with a few of the difficulties and these are when levels are elevated rather than high. My grandson is on diet and has higher levels, sometimes because he has sneaked something extra which is something children do.
Do NICE think these symptoms disappear at 18? The evidence from PKU sufferers demonstrates this is not the case, they do not stop at 25, they do not stop at 40, PKU is a lifelong condition!

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A decision based only on cost is completely unethical, KUVAN will not be suitable for everyone but everyone it is suitable for should be able to access this, diet is not a treatment it was for many years the only way to manage the conditions and make sure that suffers had as little detrimental effect as possible.

Treatments have moved on and there are treatments that can provide sufferers with the ability to maintain levels within a fairly normal diet.

Q10. I think KUVAN should be offered to all suffers who respond including pregnant women.

Q11. I have no direct knowledge

Q12. I have no direct knowledge

Q13. The ability for people with PKU to eat a more normal diet is not the primary reason for me supporting KUVAN for all, it is the associated impact of this. I would like to add the following thought, why on gods earth would anyone in their right mind wish to stop a person over 18 from enjoying a better lifestyle for those living with PKU and have responded to Kuvan favourably.

Respondent 79

Q1.I do not agree with stopping access to Kuvan at age 18.

Q2. I appreciate the idea of bringing this medicine to the UK and its definitely the foundation to build on. However stopping it at an age like 18 is simply quite silly. It would be such a unnecessarily drastic change to living at a time in your life when you're quite angsty or anxious just as a general premise and no longer being able to eat food you've eaten your whole life brings social challenges too as the restaurant you might eat with friends or a partner is no longer viable.

Q3. NICE's statements are contradictory

Q4. No personal experience but I'm sure there are a very unfortunate few who have.

Q5. Yes I agree.

Q6. I understand especially in a pandemic that you have to think economically. That's practical however the whole point of Kuvan isn't just too make money so to speak. It's about providing a medication that allows people with PKU to live a balanced diet and life without having to worry about what they can and can't have. I personally have had many nights where I've had to support my partner whose been upset or crying because she's struggling with her food whether it's because she's able to eat enough or the food is too repetitive and the same thing everyday then factor's in to other aspects of her life.

Q7. Yes I agree. I will also say that adults definitely struggle too. My partner especially struggles with both anxiety and disordered eating as a result of pku. She has struggled her whole life sometimes a little and other times like currently a lot. It really impacts her whole week/day to day mood and general health. She panics about what she's eaten and how much she's had. I spent two months last year caring for her when I wasn't at work to make sure she's okay.

Q8. The costs continue when you're older because of the other mental health effects that take part in pku. Anti depressants, councillors, metabolic team. It all adds up.

Q9. I don't think they've properly considered treating people fairly in this case. PKU is very difficult to manage even if you're in an OK financial situation. I can't imagine how much more difficult it is with more underlying conditions or difficult living circumstances.

Q10. Because of these high levels there is a increased chance of the child being born with difficulties and therefore living a much more complex life than necessary. It would be incredible vital to allow mothers the support they need via Kuvan to avoid this.

Q11. As said earlier there's a foundation to build on with Kuvan idea for u18s. Allowing females this medicine during these parameters would be crucial and so incredibly helpful it almost goes without saying.

Q12. That is something I think NICE should re look at and also ask people in such situations about their experiences to gauge what they'd need.

Q13. One step forward with bringing Kuvan. Two steps back with the cut off at u18s.
There is definitely an outcome that works for all involved it just requires time, compassion and an understanding. I really look forward to a positive response and hope this can come to fruition.

Respondent 80

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. If the proposal goes ahead my grandson will have lived half of his life with the benefits of KUVAN at a time when he is transitioning into independence and adulthood. I know from my experience with my own son, who has not got any additional needs this was a very challenging time.

Young adults have so many changes and challenges that the majority place no priority on the food they eat, preferring to grab takeaways and easy to prepare processed foods.

There would seem to be no consideration of the difficulties stopping at 18 would bring the only factor considered is the cost. There are fundamental concerns that his would be profoundly damaging to a young adult. The affect on their ability to maintain studies/jobs, ability to manage social interactions will be impacted negatively.

It is unethical to remove standard foods such as bread, pulses - basic foods for most people that will allow someone with PKU to eat a more "normal" diet which is much easier to organise both at home but also and much more importantly at this age when out in social situations.

Q3. I do not agree with NICE's view

Q4. . I have spoken to and have friends via the NSPKU and the PKU community that are adults who were advised to stop the diet. Examples of the types of issues they face are
*depression
*inability to focus
*headaches
*cognitive executive function impairment
* brain fog
* low energy
*neurological pains in the body
*general ability to cope
*anxiety
*difficulty understanding instructions
*poor memory
*lack of concentration

The ability to hold down a job, manage your own affairs and home, complete studies would be massively impacted by the above and the expectations that young adults will manage on diet alone is naïve at best. There is a wealth of evidence that demonstrates that adults struggle to maintain recommended levels even when on diet as the diet is so difficult to maintain

Q5. Absolutely, as a grandfather I actually reduced my work hours to support my son and his wife and to support my wife, so they could both work without worrying about additional care for the children, one of the main reasons for this is because of my grandsons PKU.

Constantly trying to balance everyone's food so that meals are similar means meals take longer to plan, shop for and prepare.

School has a Health plan in place but on any discussion with a teacher the response is oh it's like gluten free isn't it?

Waiting for the results of a blood spot knowing that might mean a change in exchanges and therefor planned meals for the week is at best frustrating. Most families can plan a meal and not worry, a change in levels can mean the whole weeks food changes not just one meal but 3 meals a day and any snacks.

Q6. Yes of course the affect of treatment is holistic and affects so many within the family. As mentioned above I reduced my hours of work, I was fortunate enough to be able to afford to do so but that has of course had a massive impact on our income levels and we are more financially restricted than ever before.

Q7. . I do agree with a few of the difficulties and these are when levels are elevated rather than high. My grandson is on diet and has higher levels, sometimes because he has sneaked something extra which is something children do.
Do NICE think these symptoms disappear at 18? The evidence from PKU sufferers demonstrates this is not the case, they do not stop at 25, they do not stop at 40, PKU is a lifelong condition!

Q8. He has had additional support which I have no idea regarding the costs although I imagine they are significant

Q9. There is a basic lack of equality in the cut off of 18, people with PKU face sensory and cognitive impairment from elevated levels regardless of their gender or social/economic status. PHE attacks the brain regardless of age and causes issues that impact all people of all ages differently.

A decision based only on cost is completely unethical, KUVAN will not be suitable for everyone but everyone it is suitable for should be able to access this, diet is not a treatment it was for many years the only way to manage the conditions and make sure that suffers had as little detrimental effect as possible.

Treatments have moved on and there are treatments that can provide sufferers with the ability to maintain levels within a fairly normal diet.

Q10. I think KUVAN should be offered to all suffers who respond including pregnant women.

Q11. I have no direct knowledge

Q12. I have no direct knowledge

Q13. The ability for people with PKU to eat a more normal diet is not the primary reason for me supporting KUVAN for all, it is the associated impact of this. I would like to add the following thought, why on gods earth would anyone in their right mind wish to stop a person over 18 from enjoying a better lifestyle for those living with PKU and have responded to Kuvan favourably.

Respondent 81

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I think it’s a cruel thing to expect someone when they reach 18 to go back to the most restrictive diet that they left behind previously. To deny an adult a drug available to under 18’s especially at a very crucial time of life when embarking on managing their diet themselves at Uni or work is a mean and unkind thing to do. What other drug to you take away from someone when they become an adult if their condition hasn’t changed!

Q3. NICE's statements are contradictory

Q4. I have seen my granddaughter suffer all her life, struggling to maintain her levels to ensure she reduced ‘brain fog and depression is a daily struggle.

Q5. The diet is a nightmare. Unless you have witnessed a person with pku’s struggle with maintaining levels when trying to live in the real world is unbearable especially for caters to witness. I’ve seen my daughter cry at the sadness she feels when having to say no to her child who just wants what the other kids have. Food shopping is no pleasure, eating out is stressful. Educating others who think its just a vegan diet is frustrating. Cooking different food with such a limited choice is depressing. Caters of PKU children lose the spontaneity that other parents have.

Q6. PKU has an effect on the whole family. Guilt is an emotion that all family members suffer because they cannot give the person with pku the same food that they can eat.

Q7. The above statement is correct but with the added comment that the pku person suffers with guilt when they eat something they shouldn’t. Or if they eat secretly.

Q8. It’s a daily overriding cloud on the person that shadows all that is good in someone’s life.

Q9. There’s nothing fair about denying a person a drug that’s been available to most other adults in many countries for the last 12 years. As a rich influential country, the Uk should feel shame on their attitude to people with PKU.

Q10. Nice should do the right thing, all children should have a mother or father who are the best they can be without having the burden of managing a diet whilst struggling with a pregnancy or once born a baby. Women are stressed enough when pregnant. But the risks to the unborn child from phe levels that are out of control. Nice do not seem to have done their research on PKU and pregnancy

Q11. I know my granddaughter is scared stiff about damage to any child she conceived because she has PKU

Q12. It’s all about the money! If it’s not coming out of their budget for medication, it’s someone else’s problem.

Q13. The panel who made the decision clearly know nothing about the difficulties of such a cruel condition because people with PKU look the same as everyone else. they assume it’s just a diet and people don’t die of it!

Respondent 82

Q1. I do not agree with lower dose only for milder forms /best responders of PKU. I definitely do not agree with stopping Kuvan at 18.

Q2. I think the proposal to stop treatment at 18 is ridiculous, discriminatory and cruel. I find it hard to believe it is even legal to withdraw treatment from a patient on the basis of age. There is plenty of evidence that shows the brain is not fully developed until around 25 years. In addition to this, there seems no discussion on how you would stop the drug at 18, whether counselling to the patient would be provided, how you would expect someone at 18 to be able to return to a restrictive diet after enjoying a more relaxed diet etc. There was no mention of the mental health of the 18 year old who is going to have his/her treatment/food stopped at 18 - it is a completely absurd suggestion and a shame NICE have no commonsense or empathy for the patients they are alleged to serve.

Q3. I do not agree with NICE's view;NICE's statements are contradictory;I am disappointed NICE believe it is acceptable to take risks with young peoples' brain development, their mental well-being and their quality of life.

Q4. My son is a teenager so I have no experience or knowledge about long-term brain damage in adults. However, it is a well-known fact that PKU patients have a reduced IQ to their peers and other slower neurological reflexes albeit these may not obviously show.

Q5. PKU is an orphan disease and of course patients/carers want a treatment that is not completely dietary. There is nothing more cruel than having a treatment marketed in this country which our own healthcare providers refuse access to. I am appalled by the lack of effort from the NHS and NICE to obtain access to this drug for their patients.

Q6. The NHS/NICE do not seem to value PKU patients. This is quite obvious from their complete failure after 12 years to obtain access to this treatment. Has NICE taken into account how unworthy they make PKU patients feel. Patients in general are not 'economic' but it seems only patients with rare diseases are made to feel unworthy of the cost of treatment. This is discriminatory. The fact NICE only want to pay for the lower dose for best responders is discriminatory against severity of disease. In addition, this goes against the manufacturer recommendations for dosing, of which this country gave a market approval.

Q7. I agree there is a dire need for treatment to improve PKU symptoms and lower phe levels. My son is on Kuvan and is less tired and has a much improved concentration span.

Q8. There is plenty of evidence from patients desperate for treatment - their pleas and struggles with the diet are being ignored. NICE are quite aware of the number of PKU patients who are anxious or depressed.
The behaviour of the NHS and now NICE to avoid funding treatment for PKU patients is disgraceful. This most recent proposal, although welcome for the very few patients lucky enough to respond at the lower dose and under 18, has severely depressed me. I can only imagine how upset and distressed the PKU population are who do not manage to fit into this tiny opening of treatment.

Q9. I think NICE only considers money. There is no equity in their recommendations - it is age discriminatory, severity of disease discriminatory and discriminatory to all other groups they choose to deny treatment to including pregnant women. We are living in one of the richest countries in the world and being denied treatment available in almost every country in the world - this is discriminatory.

Q10. This is the most shocking recommendation yet, which even the NHS agreed to fund. I think NICE should not take risks with unborn children when there is plenty of evidence regarding the teratogenicity of high phe levels.

Q11. Do the right thing and provide access to Kuvan to women planning pregnancy; women with PKU deserve help to have a safe pregnancy and healthy child. They deserve some peace of mind throughout this extremely difficult time when they have to drastically reduce their phe to protect their unborn child.

Q12. The fact that NICE are not prepared to help women have safe pregnancies is outrageous and a risk they seem prepared to take.

Q13. I think it is a shame that NICE works against the patients they claim to serve. They have completely failed in their duty of care to PKU patients. They have failed to provide access to novel treatments. This is not a discussion about the best healthcare for people with rare diseases and their optimal outcomes, it is simply about saving money.

Respondent 83

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. The stopping of kuvan at age 18 is an in-humane decision. Brain development is not complete at the age of 18. With this aside, one of the most difficult hurdles I've faced in my PKU journey is that of motherhood. Having Kuvan could have dramatically changed my journey from conception, which was meticulously planned, to the safe arrival of my first child. I have suffered physically and mentally ALL my life due to struggles with my PKU diet which could have been prevented with treatment of Kuvan. I'm 30 years old, and still facing these symptoms- They do NOT stop at 18.

Q3. I do not agree with NICE's view

Q4. The way that high phenylalanine levels make me feel, is that of my brain slowly fogging up and shutting down. I believe there is huge damage that can occur after the age of 18.

Q5. Some relief from the diet is essential in order for the PKU patient & carer to live a normal life.

Q6. *[no response given to this question]*

Q7. I have suffered with almost All of these symptoms. They have controlled my life since my teens until now. Resulting in regular health & mental health issues.
The main symptoms I suffer are, anxiety which on 2 occasions has lead to depression. Extreme headaches resulting in time off work & numerous trips to the GP over a number of years. Fatigue, and heightened emotional state is something I've lived with forever and has put tremendous amounts of strain on relationships with friends and family. Brain fog and loss of focus are also something I suffer with day to day. Feeling as though I can't engage my brain in order to complete simple tasks also leads to many difficulties, ESPECIALLY in adult life where Im required to focus and make critical decisions on behalf of myself and my Son.

Q8. Being off diet causes so many issues with health & mental health, resulting in excessive amounts of money being spent on time required by GPs dealing with Mentally/physically ill PKU patients, as well as extra staff involved in helping at school with PKU pupils that struggle due to high levels etc. Not to forget the extortionate amount that low protein foods and supplements cost the NHS. The answer is very simple. All PKU patients should be given the opportunity to take Kuvan, to improve the life and wellbeing of individuals from early life & all through adulthood. Taking away a treatment after a patient turns 18 is inhumane, and would result in treacherous set backs for PKU patients in adult life both mentally and physically.

Q9. It is simply NOT fair to offer treatment to individual parties.

Q10. Kuvan during maternity and conception would have made it a much more celebratory process as it is for everyone else. The is a basic human right.

Q11. Essential.

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 84

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. If the proposal goes ahead my beautiful son will have lived half of his life with the benefits of KUVAN at a time when he is transitioning into independence and adulthood. At the moment as a young child entering adolescence he struggles with being 'left out' or being 'different'. If he then had the flexibility and benefits of KUVAN, to feel like he belongs and then for that to just be taken away from him at such a vulnerable time in one's development is in my opinion, just cruel.

Young adults have so many changes and challenges as it is and the majority place no priority on the food they eat, preferring to grab takeaways and easy to prepare processed foods. There would seem to be no consideration of the difficulties stopping at 18 would bring, the only factor considered is the cost.

There are fundamental concerns that his would be profoundly damaging to a young adult. The affect on their ability to maintain studies/jobs, ability to manage social interactions, it could interfere with life decisions that are made at this age. All impacted negatively.

It is unethical to remove standard foods such as bread, pulses - basic foods for most people that will allow someone with PKU to eat a more "normal" diet which is much easier to organise both at home but also and much more importantly at this age when out in social situations.

Q3. I do not agree with NICE's view

Q4. I have spoken to and have friends via the NSPKU and the PKU community that are adults who were advised to stop the diet. Examples of the types of issues they face are
*depression
*inability to focus
*headaches

*cognitive executive function impairment
* brain fog
* low energy
*neurological pains in the body
*general ability to cope
*anxiety
*difficulty understanding instructions
*poor memory
*lack of concentration

The ability to hold down a job, manage your own affairs and home, complete studies would be massively impacted by the above and the expectations that young adults will manage on diet alone is naïve at best. There is a wealth of evidence that demonstrates that adults struggle to maintain recommended levels even when on diet as the diet is so difficult to maintain

Q5. As a mother to a son with PKU i felt i would never be able to go to work full time and trust someone else with him, i was constantly anxious and worrying as i wasn't sure if others would understand or comprehend his diet management. So much so, my mother in law, my sons Grandma actually left work to support myself and husband so we could both work without worrying about additional care for the my son (and other children), one of the main reasons for this is because of my my sons PKU.

Then when my son with PKU was old enough to go to school and we had to have discussion after discussion and plan his food and health plan i would spend my day in constant worry incase they rang.

In terms of home life its a Constant battle trying to balance everyone's food so that meals are similar, so my son doesn't feel like he is different, which means meals take longer to plan, shop for and prepare. Which is fine but when you've spent the day at work, your mentally and physically exhausted and you have other children and family members to look after to it really is draining.

School has a Health plan in place but on any discussion with a teacher the response is oh it's like gluten free isn't it?

Waiting for the results of a blood spot knowing that might mean a change in exchanges and therefor planned meals for the week is at best frustrating. Most families can plan a meal and not worry, a change in levels can mean the whole weeks food changes not just one meal but 3 meals a day and any snacks.

Q6. Yes of course the affect of treatment is holistic and affects so many within the family. As mentioned above grandparents left work.

Q7. I do agree with a few of the difficulties and these are when levels are elevated rather than high. My son is on diet and has higher levels, this is sometimes due to him sneaking food, which of course is what children do but this can be so dangerous for him.

I feel my son suffers greatly mentally due to his condition, whether it be higher levels or the fact he feels like he is different and isn't normal. All which could be helped massively by KUVAN ... However ...

Do NICE think these symptoms disappear at 18? The evidence from PKU sufferers demonstrates this is not the case, they do not stop at 25, they do not stop at 40, PKU is a lifelong condition!

Q8. He has had additional support which I have no idea regarding the costs although I imagine they are significant

Q9. There is a basic lack of equality in the cut off of 18, people with PKU face sensory and cognitive impairment from elevated levels regardless of their gender or social/economic status. PHE attacks the brain regardless of age and causes issues that impact all people of all ages differently.

A decision based only on cost is completely unethical, KUVAN will not be suitable for everyone but everyone it is suitable for should be able to access this, diet is not a treatment it was for many years the only way to manage the conditions and make sure that suffers had as little detrimental effect as possible.

Treatments have moved on and there are treatments that can provide sufferers with the ability to maintain levels within a fairly normal diet.

Q10. I think KUVAN should be offered to all suffers who respond including pregnant women.

Q11. have no direct knowledge

Q12. *[no response given to this question]*

Q13. The ability for people with PKU to eat a more normal diet is not the primary reason for me supporting KUVAN for all, it is the associated impact of this.

The mental health benefits of having well maintained levels with help with social relationships, the ability to function well at work and progress within ones chosen field. These are not big expectations they are the things that the majority of people take for granted but is not the norm within the PKU community.

I know KUVAN would be a dream come true for my little boy, it would literally change his life. Physically of course but more importantly mentally. And now I'm as a mother to a boy who i know would absolutely be ecstatic to start KUVAN, is having to make the difficult decision and weigh up pro's and con's for something that could improve my sons life, as to whether or not he should have it. As the thought of it just being cut from him at 18 is heart-breaking and potentially too much of a risk. His mental health would just tumble and i know once he's allowed the freedom of a 'normal' diet he wouldn't be able to go back to a 'pku diet' which is also damaging.

Respondent 85

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Allowing children access to kuvan and then taking it away at 18 is simply cruel and it will have devastating effects on young people.
The idea of allowing children to grow up learning to live with pku, with the added assistance of kuvan and then taking it away right at the brink of them potentially moving out and gaining greater independence, seems tantamount to torture. I can only see it leading to huge issues with mental health and a failure to adjust to the diet. I can only speak from my own experience, but I am well aware that even relaxing the diet a little, makes it so much harder to get back on it.
The use of kuvan during childhood and adolescence should absolutely be celebrated, but we can no way celebrate the offer on the table. If you had offered it to me in my teen years and I knew it would be taken away at 18, I doubt I would have taken it. I tried hard to follow my diet but the stress of following such a strict diet led me to disordered eating, as I felt not eating was a much better option than the stress of sticking to it.

Q3. NICE's statements are contradictory

Q4. I believe, having struggled to control my levels throughout my late teens and my 20's and beyond, has very much affected me in many ways. I have a tremor in my right arm that I developed in my early 30's, I have no family history and the tremor is noticeably worse when my levels are high. I have terrible concentration; I suffer from depression and anxiety and I still battle with avoiding food altogether. If I could not eat, I would be very happy. I shut myself away from socialising because I am embarrassed by my condition. Having had 2 healthy pregnancies, I can confirm, I feel so much better when my levels are controlled, I just struggle to control them often. I describe high levels as wading through a fog, I really don’t feel myself at all.

Q5. *[no response given to this question]*

Q6. I have pku, so I’m not caring for anyone with it, other than myself but I can say that organising the diet for myself is a full time job in itself. It takes a lot of planning, baking, researching and education I can only imagine how difficult that is to manage for children.

Q7. I would argue that I experience all of those things too, when my levels are high and I am 37 years old. If children should have access, then I would argue, so should adults.

Q8. As previously mentioned, I believe pku effects my quality of life in many ways. I suffer from headaches, poor concentration, low mood, anxiety, a tremor and disordered eating. I have experienced panic attacks around food and social situations where I am forced to weigh and measure what I’m eating. I feel deeply embarrassed when people start asking questions. I have extreme anxiety around receiving the results of blood spots, which I know is ridiculous but I can’t talk myself out of. I feel entirely consumed by my diet and my phenylalanine levels. It takes over my whole life and I would argue is hugely determinantal to my quality of life.

Q9. I do not believe NICE have considered treating people fairly at all. I can only speak on behalf of women maintaining a strict diet through pregnancy. The precon diet is so difficult. The pressure you are under is incredible. You do 3 blood spots a week, and the results of those blood spots alter what you can and can’t eat. My dietician would call and my level would be high and suddenly I have to drop down to 0 grams of protein. That was made all the more fun when a gp told me I couldn’t have my prescription because I can buy all my food at the supermarket. Which I know, many of us are told repeatedly and it is inaccurate. Every high level sends a panic through you, as to what damage you are doing to your growing baby. Morning sickness makes your levels rise. My levels shoot up just before I come down with a bug even something as simple as a cold and the only thing I can do is eat less but maintain my calorie intake. Your whole life revolves around the diet and you are already exhausted. I don’t think I can fully do justice, to how hard this time is. I would love a 3rd baby but I genuinely don’t think I could do it again. Kuvan would be an absolute blessing.

Q10. Kuvan should absolutely be made available for pregnant women. Every woman I know with pku, that has had a baby, can tell you what a struggle the diet is. High levels that you just can’t get under control due to sickness or illness, could be helped with kuvan. The peace of mind this would give is astronomical, let alone the benefits to the growing baby with the reduction in risk.

Q11. I was always very anxious about falling pregnant while off diet. Kuvan would’ve taken some of that stress away. I did fall pregnant with my second while off diet and it caused a lot of emotional turmoil and I spent the whole pregnancy worried I had caused damage in those early weeks. It effected my sleep, I suffered with insomnia for most of my pregnancy due to stress. I also experienced panic attacks at various stages. I didn’t see friends or family due to anxiety and those relationships are still struggling.

Q12. *[no response given to this question]*

Q13. I think the draft recommendation by NICE is discriminatory. I don’t feel that the effects of pku in adults has been given fair consideration, as with the impact kuvan would have to the quality of life to all those with the condition. Having experienced 37 years of living with this condition, I can tell you that increasing our freedoms would be an absolute blessing and I personally might be able to enjoy food without the anxiety or stress. Our diet is extreme and thoroughly challenging, it is so much more than ‘just a diet'. We are doing our best with the limited support we can receive at times. There is a genuine excitement about the prospect of kuvan being more accessible for children, but we plead with you to not leave us behind and as a bare minimum, please reconsider taking kuvan away when children turn 18, it is a truly terrible idea.

Respondent 86

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. As parents of a 7 year old boy with PKU, we are fully aware of the benefits that Kuvan offers those children and adults who are lucky enough to already receive this medication. Given the current proposal, we would not feel comfortable allowing our son to take Kuvan, in the knowledge that it would then be stopped once he reached 18. At that age he would be a headstrong young man, and we are sure that convincing him that he would need to return to the same strict diet he followed as a young child, would be beyond difficult. He would have become used to the many benefits that Kuvan allows - more freedom with food, more freedom with eating out at restaurants, and just a general all round feeling of being a little more 'normal' - all things which are important to everyone, but especially teenagers. It feels barbaric that there is a drug which would improve a child's life, but which would then be cruelly taken away as they reach 18 - a crucial milestone where many would be living away from home, going to University or starting a career. As parents, we are both shocked and upset at this decision.

Q3. I do not agree with NICE's view

Q4. We have experienced PKU life for just over 7 years now, and have met a variety of wonderful and supportive people who have helped us learn how to live with this rare and difficult condition. During these years, we have spoken to several adults who have stressed to us the importance of making sure our son stays on the diet FOR LIFE, because of their own experiences of coming off the diet, and then struggling to function in day-to-day life. Brain fog, anxiety, mood disorders and lack of concentration being just a few of the things they all mention. Some of these effects are, sadly, quite evident from their manner or behaviour, and it's served as a stark warning to us. We will do everything within our power to ensure our boy sticks to the diet for life, but are under no illusion that this will be difficult. This is why Kuvan for children up to 18 - AND BEYOND - is so crucial.

Q5. There are no days off with PKU. Every meal, every day, is planned and prepared for in advance. This is combined with having to ensure that those who help with the care of our PKU child - grandparents, school, friends - fully understand what the diet entails and what he is or isn't allowed to eat. This is hard enough to monitor on a good day, but when Phenylalanine levels are raised - often for unobvious reasons - the diet has to be even closer scrutinised, and the mental and emotional stress it puts parents and carers under is increased. As well as ensuring the Phe levels are controlled, PKU comes with it's own social dilemmas too. We can't just let our child go to a friend's house for tea, or help himself to a buffet at a children's party. There are always restrictions and limits, and that is difficult for a small child to understand, and upsetting as a parent/carer to have to enforce. Having Kuvan, and thus having a higher protein allowance would help massively with these situations, and make our son feel a little less different on these social occasions. BUT, as stated above, whilst the decision would be to stop Kuvan at 18, we are unable to even consider Kuvan as a treatment, because the detrimental effect it would have on his mental health (and his brain if he chose not to return to diet) outweighs the advantages that Kuvan would offer him for the 11 years he would be allowed it. It feels very cruel that we have to even make that choice, especially when we're fully aware - and often see from Social Media - the obvious benefits that Kuvan brings to PKU children's lives.

Q6. Absolutely, yes! As well as our PKU son, we have a non-PKU daughter. Whilst we try our very best to ensure that she does not miss out on anything because of her brother's PKU, sadly it does happen. That visit to an Ice Cream Parlour or a Pick n Mix at the Cinema is just not always possible. It sounds very over indulgent, but these 'treats' are important to children, and having to restrict them because it's unfair having our son watch his sister and / or us enjoy food he can only dream about eating, is hard. We spend a good deal of time on our son's PKU - it dominates where we go out as a family, where we go on holiday, where we can stay - i.e. hotels or self-catering accommodation - restaurants we can / can't eat at. Our daughter is incredibly supportive of her brother's condition, but we can wholeheartedly say we would do things differently - and more spontaneously! - if our son had a higher protein tolerance.

Q7. When our son's Phe levels are high and out of range - due to illness or any unobvious cause - we notice a very clear change in his mood. He becomes over-emotional and irrational, and often we spot the warning signs before we've even had the blood result confirmation back! This has got worse the older he gets, and from speaking to other PKU families, we understand it is likely to continue to be an issue. It is massively distressing to us, as parents, watching our son become frustrated and upset at something which ordinarily, he wouldn't give a second thought to. It fills us with worry for the future, particularly with regards to his mental health. The nice advantages of Kuvan - i.e. being able to eat more 'normal' food - are clearly appealing, but as parents, having a drug which actively helps to keep Phe levels in the safe range, and thus avoiding the obvious physical and mental effects which come with them being out of range, is priceless. We would urge NICE to recognise these health problems, and further still, appreciate that the time and cost of treating, for example, the mental health aspects of PKU, will far outweigh the cost of Kuvan in the long run.

Q8. Our son has very obvious anxiety issues when it comes to school. He's 7, and so at this stage we're not sure if this is a personality trait which he will grow out of, or if it's something more serious which is connected to his PKU. He has amazing support from the school, but extra time and care is invested in him, and this will only increase if this develops into a greater issue as he gets older.

Q9. We feel very lucky that we are physically, mentally and financially able to support our son, but we know others are not as fortunate. We have seen first hand, a number of families suffering hugely because of their family arrangements, be that due to low incomes or existing / additional disabilities within the household. Children and young adults with PKU are suffering through no fault of their own. The treatment for PKU is a strict diet - that is hard work and comes with a massive level of responsibility. Where people are struggling already, this can simply be too much. NICE do not seem to have taken these inequalities in to account when making their decision to restrict Kuvan to children up to 18. We need - and some more than others - a lifelong source of support. Taking it away from a young adult at 18 is going to cause a car crash of emotions and difficulties, and some families or young adults are not going to be equipped to deal with that.

Q10. When our son was first diagnosed with PKU at 10 days old, one of the first things our consultant said to us was "be glad that he's a boy, because girls with PKU have it a lot harder". He was completely right, and some of the struggles we have heard of, particularly with regards to maternal PKU is quite horrifying. NICE must support PKU females, especially those aged 18 and above who may find themselves soon wanting to start a family of their own - this is when they need the support the most!

Q11. Please see above.

Q12. Please see above.

Q13. Our final plea, as parents to a very clever and happy 7 year old PKU sufferer, is just give us the chance to make his life easier and more enjoyable. It would be barbaric and unethical to treat a child for 11 years with a drug which has been proven to help so many, and give a whole new lease of life and freedom for those who are lucky enough to respond to it, and then take it away from them when they're at an age where they need it most. The PKU community have waited, and fought, for such a long time to get access to treatments which are widely available across the world, and it feels like a cruel twist of the knife to finally say, they can have it, but they have to stop it again at age 18. We are sure the cost benefits, with regards to the reduced need for (very expensive!) prescription food, less necessary social/health interaction, less mental health treatment, and less hospital intervention, would soon become apparent, if only the PKU community were given the chance.

Respondent 87

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Although it is amazing news for pku children to be able to receive this drug it is also is wrong to cease treatment at the age of 18 as children will then need to have to reset the extremely strict diet. My child who is 2yrs of age & only on 3 1/2 exchanges a day, if she was a responder & it massively increased this, her diet would be some what a little more relaxed, however to be then robbed of this treatment at 18 & not have memory of this strict diet she once was on at 2yrs old & the struggles with this diet, i feel this would have such a negative effect on any 18yr old with PKU, They would certainly struggle mentally, suffer with anxiety,depression, & it become really challenging for them. It is like putting a diabetic on their path to a healthy diet & insulin to treat it, to then suddenly take the insulin away from them would be unethical!

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. I agree. The daily struggles, stress & anxiety as a parent of PKU is on another level, the daily worries we face really impact on our life, our work life, and any spare time is spent managing this diet & trying to prepare for the days ahead is such mammouth & overwhelming task.

Q6. Yes. We have family members that are reluctant to get involved with the care of our PKU child in fear of managing her diet & getting it wrong & thr additional cost that may incur. It restricts us from doing 'normal' family activities such as going for a family meal as very little places can accommodate her complex needs. Even just being spontaneous and just going out for the day is then followed by fear,anxiety & stress as it then becomes a task,we need to plan food/drink for that day, which then can prevent us from going places and takes the fun out of a fun day out

Q7. Yes I agree

Q8. *[no response given to this question]*

Q9. No, if you are not financially stable, hitting the age where you then have the drug taken off you as a young adult on lower income amounts, these people would be massively disadvantaged as its not been taken into consideration the cost of this extremely restricted diet, such as the prescription foods etc.

Q10. They should make kuvan available to maternal PKU women.

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 88

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Since our daughter ***** is only coming three I have no direct dealings with a teenager living with PKU, however since we found out she had PKU it has totally changed our way of life. We constantly have to monitor ***** food intake and make sure she takes her supplements every day which are really not nice to smell or taste. The restrictive nature of ***** diet is hard to take, especially when you can see her as she is getting older enquiring about foods that we have to tell her she cannot have which is soul destroying. I am so proud of how our daughter copes with little food options she can have daily but if she was a responder to Kuvan it would be life changing, the thought that we could walk into a restaurant and have her eat from the menu would be a fantastic feeling. It would be unimaginable however if she was to get Kuvan and then have it taken away when she would turn 18, the damage that this would do to her life would be unmeasurable. The returning to a highly restrictive diet would be a catastrophe for her mental well being and quality of life. The chance to eat normal food is something that we all take for granted but for this to be taken away from someone with PKU when they turn 18 due to cost is deplorable and really unethical.

Q3. I do not agree with NICE's view

Q4. I do not have personal experience with brain damage in adults but I do know that if PKU is left untreated in adults it can cause brain fog, depression and poor memory. I truly cannot understand why our fabulous healthcare system does not take a rare genetic condition like PKU seriously, no one should be left behind regardless of cost. We have a close friend who is a nurse that works with brain damaged patients and it does not bear to think about ever wanting to have to deal with an adult with brain damage.

Q5. I fully agree with the comments above, PKU is on your mind all day every day. I also find that it has an effect on carers mental health as well, it isn't an illness that last for a few days. It is a life long condition that needs to be kept on top off at all times.

Q6. Yes all aspects of PKU and who all are touchpoint with someone with PKU should be taken into account.

Q7. I fully agree with these comments above.

Q8. I don't think that it is hard to work out what effect it would have on the quality of life, clearly the answers to this is the foundation of what PKU is and what are the issues if PKU is not treated.

Q9. It makes me sad and angry that it boils down to the cost effectiveness, I think this is wholly unjust and morally wrong for it to come down to money. There is a total disregard of the adult population with PKU, if PKU wasn't a rare disease it would be funded with no questions asked.

Q10. NICE should recommend that Kuvan be available for women with Maternal PKU

Q11. I am no expert but having read articles online and the benefits that Kuvan could have then it is a no brainer for it to be made available. If it is able to prevent harm to an unborn child I don't know what the delay is in making it available.

Q12. Clearly it needs to be looked at in terms of the damage that it could have to the children.

Q13. I would urge that NICE would recommend the funding of Kuvan for adults with PKU. We have one of the best health services in the world but the fact that it isn't funding Kuvan while other countries around the world have been using it for years. The life changing nature of this drug for people with PKU is vitally important and I pray that common sense prevails and morality prevails in approving this drug.

Respondent 89

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. PKU does not magically disappear when you turn 18. The implications of stopping treatment will have a negative impact on the persons life causing higher phe levels during an important time in their life where they may be studying a-levels or other exams and learning to live a more independent life with their diet. If their pku diet has to change over-night it will take time to adjust to living with lower protein exchanges whilst managing the change in phe levels and adjusting the diet accordingly. This would be very stressful and they would need much more support from parents/hospital at a time when they should be more independent.

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. Having more protein would have a positive impact for my son. My son is on 7 exchanges and it affects so much of his life. Every birthday party he's been to he has only been able to eat what we give him to take with him as there is almost always never any food he could eat which was provided by the host. This leaves my son feeling sad/different/left out. There's only one restaurant where he can go to which serves food he currently can eat which is not french fries so we don't go out much as it's unfair he only can have a small amount of chips. He's unable to go to school dinners as they don't provide suitable options for him (except chips) so what's the point in going. At Easter he has to ration his Easter eggs so he doesn't eat too much protein whilst watching his siblings eat all theirs in one sitting. He constantly feels deprived of food enjoyment. If he was able to have more exchanges by taking kuvan then he would be able to part fully in social food experiences and therefore we would feel less guilty/sad as parents. It's stressful managing the diet having to always think what has he had to eat so far and what he can still have. You never switch off.

Q6. I quit my job after my son was diagnosed with pku as it was difficult to trust other people to adequately manage his diet. As he's gotten older I've remained at home. Having to make low protein foods to fill the gap that he can't make up with normal higher protein foods, manage his various prescriptions each month for 3 different delivery companies, plan his meals, doing blood tests and liaising with his dieticians. It's time consuming and stressful especially when my child is an extremely picky eater and when there is a lack of food options that he can have or likes makes it more difficult. I feel the decision to approve Kuvan is not just about the person with pku but also those closest who help them live their life so they stick to the diet to keep their phe levels in the right place.

Q7. My son has always had good phe levels until this year. He has had frequent out of range results which can't be easily explained. If he was on Kuvan it could help lower them and put them back in range. He suffers from anxiety/lack of focus,restrictive eating habits (only eats a small variety of foods and doesn't like them touching each other) and has in the past had constipation for a prolonged period.which required medication to resolve. I would doubt this will disappear when he turns 18 and if he was on Kuvan it would help control his levels to allow him to be able to eat more varied foods and avoid having high phe levels in his blood and it's affects.

Q8. *[no response given to this question]*

Q9. I think it's unfair woman who are in Precon/pregnant are not able to access Kuvan to keep their phe in safe levels to ensure there are no damaging effects to the baby. I have had gestational diabetes 3 times and each time I had hospital support to ensure I kept my blood sugars in the correct range to protect my unborn baby. Both before pregnancy and during I also had to go on a special diet before and during pregnancy which is exactly the same as pku pregnant women and most importantly if I needed to go on medication to reduce my blood sugar levels that was of course prescribed. I see no reason why pku women should be discriminated against. It's exactly the same situation- to protect the unborn babies from birth defects/still birth etc from high blood levels.

Q10. The should give Kuvan to help women manage maternal pku as it is widely known that woman must strictly manage their levels in pregnancy (and precon) to avoid birth defects. Given how important this is then any help (in form of Kuvan) must be allowed.

Q11. Women who are planning a pregnancy should definitely have access to Kuvan to avoid harm to their unborn child. It is known that high levels in early pregnancy can effect the baby (just like in diabetes) and so any help to avoid that should be used.

Q12. If women with uncontrolled pku have a baby with neurological damage then the child will be requiring interventions/help from paediatricians/speech and language, occupational and physical therapists to help them which all comes at a cost financially to the nhs for the rest of child life. If the pku woman had access to Kuvan then this could have been prevented and had a healthy child requiring no medical intervention.

Q13. I'm grateful that NICE has approved Kuvan for under 18's but it feels utterly unfair that it should be taken off them at 18. It's not a disease that goes away at 18. Treatment should be for life as pku is for life. You do not take away insulin therapy from a type one diabetic when they turn 18 so why are you doing this to people with PKU. I'm disgusted at this decision to stop Kuvan at 18 . It's like dangling a golden carrot at the children and turning it to dust when they are 18.

Respondent 90

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. It would be discriminatory to allow some PKU patients access to sapropterin and then to deny access to it based on age at 18. The brain does not stop developing at 18 and your suggestions that the cost for larger than 18 year olds is flawed, in that some under 18 year olds may be significantly heavier than adults over the age of 18. To discriminate against an obese 17 year old, for example, would also be as unethical as discriminating based on age.

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. When there is a treatment that can be provided, such as sapropterin, it would be unethical to continue to expect families to act as carers, impact their own careers and life chances and ability to provide such things as higher cost foods for their PKU family members when there is an alternative treatment which would provide them with a far more equitable life. Access to sapropterin in these families would provide the opportunity to level up such families and improve their life chances and opportunities which impact on the entire family. This treatment should obviously be continued throughout the PKU patient's life so that there is never a future need for anyone to act as a carer to them.

Q6. It is vital to take into account the costs to the country and NHS overall when considering each entire family affected by PKU. The levels of stress affecting carers of PKU family members has an impact on their ability to work reliably and has a very real chance of impacting on their physical health and mental wellbeing. The costs of a PKU patient, with the expectation of having a normal lifespan, are likely considerable, when accounting for their prescription needs for supplements, specialist foods, hospital appointments, hospital transport needs, GP appointments and so on. These costs should be costed out and balanced with that of sapropterin.

Q7. I fully agree that the treatment is needed for teenagers and children to support them in coping with these unnecessary symptoms. It is equally necessary to provide the same treatment for those over 18 as they are as entitled as children and young people to the same peace of mind and life free of these same symptoms which adults, like children, do also experience.

Q8. There would inevitably be high associated costs involved in providing the right support for a child/family such as TAF/TAC meetings as just one example. More likely, however, would be that the child would slip through the net as the child would be classed as having SEND and would face the usual challenges to accessing much needed services such as mental health support appointments and access to clinical/educational psychologists. There would not be a joined up approach as no service other than the metabolic team would understand PKU and be able to differentiate between what was being caused by the struggle of caring accurately for a child with PKU and the effects on the developing brain as it is a rare disorder. The same costs would/should apply to adults over the age of 18 who would equally require very similar support services. Slipping through the net would negate the need for any costs to be applied however this would, of course, be denying care and would be unethical.

Q9. NICE has been contradictory. They have clearly evidenced that there are groups of people who could be both adults or children, who need access to sapropterin despite their expectation that this would be at too high an economic cost. When adult PKU patients are unable to control their diet for any of the reasons mentioned, the symptoms that manifest themselves at this time make re-beginning the highly restrictive diet all the more difficult to attempt and maintain, thus resulting in a vicious circle. It would be unethical and cruel to expect adults to continue to suffer symptoms when there is treatment available if only NICE were to value them highly enough to provide that treatment. I have read of evidence from pre-con diet women PKU sufferers and maternal PKU women just a few weeks into their pregnancies whose levels are evidenced as being at a dangerous level for a developing baby. In very basic terms, the cost to the NHS of a baby born with associated conditions from having developed in a PKU woman with poorly managed dietary control would likely be more significant over the course of their life compared to the cost of funding sapropterin for the PKU mother. As a PKU woman, I have had three children whilst very religiously following the pre-conception and pregnancy PKU diet. I am also on diet for life and have always been on a very well controlled diet all my life but it takes understanding of the condition and the protein content and quantity of every item that goes into your body. It is well-known that, even with understanding of healthy food, non-PKU adults struggle enormously with the self-control of even staying on a diet. My guess would be that every member of the NICE committee has at some point attempted to restrict some item of food or drink, and may even have had the support of a specially set up outside agency to support them in that quest. It is well known that all adults struggle with some form of self-control in at least one area of their life but they do have a choice. All PKU adults, including ones in the disadvantaged groups NICE has identified, have no choice but to exercise extraordinary self-control, unless they want to face the awful symptoms to arise from not following the diet or unless they have access to sapropterin treatment.

Q10. My answer to the above question hopefully shows the need for NICE to recommend sapropterin to PKU women to help them manage the risk of poorly controlled diet to unborn children. All women with PKU deserve to be offered sapropterin as treatment. Women with the even more highly restricted pre-con and pregnancy diet deserve sapropterin even more as the protection of the baby is so very important and PKU women should be supported as fully as possible in trying to protect their developing babies.

Q11. As a 48 year old woman now, I can remember being told by my metabolic clinic that, should I ever become accidentally pregnant as a PKU teenager or PKU woman, I would be offered and advised to have a termination. No other solution was offered. The psychological impact of that on a teenager and woman was considerable. Every female considers how they would cope with an unplanned pregnancy but this additional pressure made the risks even higher and the knowledge that this would be a very public situation that the metabolic team and family would need to be involved with, was psychologically negative. The worry of this never leaves a PKU woman throughout their life, whatever their life circumstances. If PKU women have access to Kuvan, the harm of an unplanned pregnancy on a developing baby need not cross their minds, in the same way as it would not have to cross the minds of women without PKU - this would then be equitable and non-discriminatory.

Q12. In very basic terms, the cost to the NHS of a baby born with associated conditions from having developed in a PKU woman with poorly managed dietary control would likely be more significant over the course of their life compared to the cost of funding sapropterin for the PKU mother. If NICE looked for evidence of this, I am sure there are children or young people who are living with the long-term physical and neurological effects of their mother having been unable to manage her incredibly restrictive, impossible diet. It is vital to weigh up the costs in NICE's calculations, if they are to be thorough and accurate in their decisions.

Q13. *[no response given to this question]*

Respondent 91

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. The difference between a PKU severely restricted diet and a Kuvan treated patient on a more relaxed diet is considered significant. Every 1 gram of additional protein in the PKU world is life changing. That is how restrictive the diet is. Therefore to remove a more relaxed diet from a child at the age of 18 is unethical at best and torture at worst. 18 is an extremely important age for children as they transition to adulthood - potentially starting university, starting a job, moving out of home and leaving parental support for the first time in their lives and NICE are expecting a child, alongside all of these significant life changing events, to also manage the transition to a severely restrictive diet. Adherence

to this restrictive diet can really only be learnt and remotely accepted if commenced at birth. Even if the diet has commenced from birth, it is still an extremely challenging diet to comply with. The impact of removing Kuvan from patients at 18 would be immense. Other countries, such as in Australia, who have recommended the use of Kuvan for babies, children and teenagers - do not see the drug being removed from a patient at the age of 18. IF you start the drug as a child, you continue on Kuvan beyond 18 years old.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. My twin daughters with PKU are currently 2 years old, therefore I can't comment from personal experience. However, the statements made by NICE are contradictory and require further explanation from NICE.

Q5. I wholeheartedly agree with the comments above. I, as a mother to 2 year old twin girls with PKU, have completely given up my career as a Chartered Accountant at a large global professional services firm. I have taken this decision so that I can dedicate my time to giving my girls the best start in life in terms of ensuring their diet management, control of their phe levels so as to reduce the risk of brain damage. Such is the level of trust that I would need to put in another individual to ensure the health of my daughters' brains, I just cannot take the risk of entrusting them in another persons care. Despite my family being explained the girls condition numerous times and the various aspects to their diet management, they still do not understand and do not trust themselves to get it right. Even when GP's and doctors are prescribing medication to my daughters, they get me to double check ingredients in medications before prescribing. My daughters are identical twins - my family have difficulty even telling the difference in the girls, let alone ensuring each child is complying with their highly restrictive diet. The result is that as their primary carer I get little or no respite. To even have a 2 hour break, I need to leave such detailed instructions with foods pre-weighed and pre-prepared in advance.

Q6. I wholeheartedly agree that NICE should take into consideration other family members. Since the day my daughters were diagnosed with PKU on 18 December 2018, PKU has been the centre of our lives. There is not a minute of any day that I do not have to think about PKU and the impact on my daughters and what they can eat and drink. I also have a child who does not have PKU - I have had to teach her to be secretive with her food so that my twin daughters do not see what she has and want it too. This is just wrong. My non- pku daughter is only 19 months older than her twin sisters and the foods that she needs to be healthy are considered toxic and are basically poison to my twin daughters. My eldest daughter needs to eat cheese, yoghurts, bread and pasta to be healthy but I can't let her eat these foods in front of her sisters. What long term effects are these eating behaviours having on my 3 daughters??

Q7. I agree with the comments above, based on what I have heard from other families with children with PKU. My daughters are only 2 and I have limited experience with the specific health problems outlined above. We do have issues when my daughters are teething or have colds or other infections - all of these issues cause my daughters phe levels to increase significantly outside of range which results in them being cranky, experience poor sleep, being bad tempered and acting out of character.

Q8. My daughters are 2 and so I have limited experience at this point. I have given up my career to solely focus on the care of the girls and ensure their diet management and ultimately control of their phe levels.

Q9. No NICE have not properly considered people with special circumstances. The PKU diet is an extremely expensive diet and also an extremely complex diet to learn and comply with. Typically the only foods in the supermarket which are low enough in protein for my daughters are the most specialised expensive foods. We are a single income family and find it really tough on a monthly basis to feed all of the family, whilst ensuring some variety in our daughters diet. Therefore I can understand that a low income family would find this extremely challenging and essentially impossible. Reading labels and translating information to phenylalanine exchanges is not straightforward and is highly complex.

Q10. I believe NICE should to be recommending the use of Kuvan for maternal women. My daughters are only 2, however if they decide to have a family some day, I already dread the impact this will have on their mental health and the health of their unborn child. High phe levels are extremely dangerous for an unborn child. What if my daughters were to fall pregnant by accident? This would have a profound and life changing impact on the unborn child.

Q11. I have no further comments

Q12. I have no further comments

Q13. Our family are currently living in Northern Ireland - what steps are there in place to ensure paediatric patients in Northern Ireland can get access to Kuvan? I would also like more consideration be given to the current recommended dosage of 10mg/kg. The current maximum dosage being recommended by NICE is 10mg/kg. Based on discussions with dieticians some patients need more than this. 10mg has been recommended based on cost. Clinicians should have flexibility to prescribe more if needs be.

Respondent 92

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. This will be extremely difficult for those on Ivan to stop just as they are heading to university and child bearing years etc

Q3. NICE's statements are contradictory

Q4. My older sister (with PKU)has long term brain damage. It affects her in everything she does and every aspect of her life.

Q5. No comment

Q6. Yes.

Q7. I strongly agree

Q8. PKU is a daily struggle. Trying to manage PKU and run a business and raise a family is so difficult.

Q9. Absolutely Not! Are adults not worthy of treatment? Are you kidding me? At an age when we are studying,looking after young children, holding down jobs and at a critical time where we are trying to get pregnant with perfect PHE levels. This is not fair or just.

Q10. Kuvan for all

Q11. No

Q12. I highly recommend they include this in their costs evaluation.

Q13. Provide kuvan for adults also.

Respondent 93

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I am obviously delighted to hear that Kuvan may be available to my daughter (1 year) but I have serious concerns about the decision to remove this treatment from her when she reaches 18. The pku is extremely limiting when it comes travel, socializing, pregnancy and in many other areas of adult life.

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. I agree, my daughter is only 1 and I have limited experience with the pku diet but I do already have massive stresses regarding keeping her safe within her phe levels.

Q6. Yes

Q7. *[no response given to this question]*

Q8. *[no response given to this question]*

Q9. *[no response given to this question]*

Q10. Kuvan should be available to all women with pku who are trying to conceive. It is essential that phe levels are controlled to ensure safe births.

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 94

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Its setting a child up to fail as a teen and adult . Also mentle health crisis as we know effects us this way . The children will not learn how important diet is and how to do restrict their relaxed diet .its wrong way round easier for kids as parent takes control as teen adult it gets harder to manage with own life troubles

Q3. NICE's statements are contradictory;I am 40 and came off diet at 18 i now can not work i have short term memory problems i have damage to my exective function lobe so planning organising following thorough things aand understanding ect . I have tried millions of times to get on diet

Q4. Yes myself and my pku partner have damage to our brainswithen the exective function area working memory .white matter and cognitive testing and have lost jobs we also have mentle health issues

Q5. My and my partners relationships/marriages broken down .

Cereing for myself is hard I also have a career because of the damage to my brain sometimes means I need supervision with things like cooking travelling ect
Working out the diet ect

Q6. Yeah I do because pku effects whole house hold time consuming and the main carer has a lot to do and my num dosent eat propley

Q7. Adults infact exsprience these alot more than a child with pku .because levels tend to be more in control when younger as a parent is in control .

So yes defently effects adults I have antidepressants and anxiety meds.
And my focus is impaired

Q8. I am living proof it effects pkuers quality of life my partners and sisters too .
It's clear that adults are over looked and left on the shelf we are the ones struggling daily

Q9. we should be allowed to try kuvan I have fibro b12 deficiency and cognitive and memory damage anxiety depression
If I'm a responder it would make my life a bit easier and feel it's unfair that they would stop it at 18 .

I was 14 when was told about kuvan b4 then and I'm 40 still waiting for something to help other than diet .

Q10. I was on 0 exchanges for 4 months both pregnancy.
That is NO PROTIEN at all .
Kuvan would have helped me a lot to be able to eat a little protien .

Also would have defently helped after having baby

Q11. As above would benefited me and sure others it's very restricted. I lost 2.5 stone in pregnancy as wasent much could eat and replyed on my partner to cook safe meals I was getting hypoclasmic.

Q12. Just that they should look into it all deeper and not focus on children

Q13. Think about adults and see it has a big impact on us anxiety depression living with a chronic condition effects us socializing because everything consists of food and drink work also .
A lot of adults have own family to care for and life issues get in the way and as a mother we find hard time to think and do for ourselves we get lost in life around us

Respondent 95

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. It as been wonderful new that kuvan is now available like all other countries but we have been totally let down by the fact that it will be stopped at the age of 18. I wonder if u could remember been a teenager yourself and now much happens in your teenage lives. Kuvan allows the pku child to eat more protein and then at 18 it's totally stopped. We all know how hard it is to do a healthy diet to loose weight and yet we have so much to choose from while a pku diet is the most limited diet your never come across.
You really haven't taken into consideration the effects this would have on a teenager
I wonder was this planned as NICE be hoping no parent will allow there child to try kuvan die to it been stopped at age 18 so that will save them money.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. Totally agree with both. It is such a difficult diet to follow. None of our family are able to help as they find it hard to understand and then I as a parent have a worry what if they give them something they shouldn't.
I had to reduce my hours at work so to be able to look after the pku diet and treatment
We have a every day fight for 4 times a day to get our daughters to drink the most horrible formulas as part of the pku treatment. As a parent I feel like the most cruel mummy as my girls are ready to vomit after each pku formula.

Q6. They should totally take it all family members into account. We dont have nice family holidays were we can eat what we like our go to restaurants unless they can accommodate pku diet which most dont. Our holidays are always self catering so there never a day off from cooking.

Q7. Yes I agree with above as My both girls struggle with every day school work due to poor concentration and slow processing speed which as also been diagnosed by clinical psychologists.
My both girls also complain of stomach cramps and constipation

Q8. *[no response given to this question]*

Q9. How can NICE say this when other countries support kuvan for all adults

Q10. NICE I really don't understand how u came to this conclusion. You must have never spoken to a pku mum to be. This is a real let down

Q11. Just speak yo pku woman who are now mums yo establishe how difficult pku and pregnancy is

Q12. *[no response given to this question]*

Q13. Please NICE take into consideration how damaging it would be to stop kuvan at the age of 18 please but yourself into the pku child/adult shoes even for a day or week to see why us patents are fighting this outcome. We have already waited years to be allowed kuvan as a prescription

Respondent 96

Q1. I agree completely with this recommendation

Q2. *[no response given to this question]*

Q3. I agree with NICE's view that there is no risk of long term brain damage in people with PKU aged over 18

Q4. *[no response given to this question]*

Q5. *[no response given to this question]*

Q6. *[no response given to this question]*

Q7. *[no response given to this question]*

Q8. *[no response given to this question]*

Q9. *[no response given to this question]*

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 97

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. *[no response given to this question]*

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. *[no response given to this question]*

Q6. *[no response given to this question]*

Q7. *[no response given to this question]*

Q8. *[no response given to this question]*

Q9. *[no response given to this question]*

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 98

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Totally disagree with this. It is so hard with children on this diet to get used to it, and even different tastes, so then to take it away and re-educate them. Also for the carers / parents. Is that not similar to taking inhalers from asthmatics?

Q3. NICE's statements are contradictory

Q4. Have they spoken to adults with PKU who have come off diet? It stands to make sense that if you explore people who are in 3rd level education, holding down a responsible job with PKU are usually on diet and controlling their levels due to issues they've had with concentration, moods, behaviour, depression etc. So people may not term this as brain damage but it definitely affects brain activity.

Q5. I totally agree with this. I myself struggled when me daughter was a baby - post natal depression, wouldn't let anyone else look after her. I was so highly strung that it affected my relationship with everyone in the house. Then yes, any other childcare, teachers, parents of friends, brownie leaders, sunday school teachers all need to be familiar with what is needed. It's a constant education. I myself am on reduced hours and it can take extra time for shopping to find items that are suitable. We are having issues post Brexit getting some of the low protein items in supermarkets due to supply issues.

Q6. Yes as this would add substantial, necessary value. I know I have books / laminated sheets at school, with my sisters and some houses where my daughter used to spend time. This means other adults are not worrying about what they can and cannot feed Abbie. When Abbie went on a Brownie pack holiday that was a lot of extra consideration for the leaders but they were happy to take my instruction and use her food to include her.

Q7. I agree with this statement.

Q8. Maybe the reason that the information is difficult to tabulate is because families, carers etc are fighting every day to do a good job and keep everything under control - therefore limiting extra help in the long term. The extra support we received from the metabolic team when Abbie was born was brilliant, we couldn't have coped without them.

Q9. Surely this cost would be worth it as then these people may need less support / care. Is it not a case if this care was offered to some of these ethnic groups so that if they wanted they could avail of the treatment.

Q10. I think this would help women with PKU. This would give them a little leeway with their levels and so minimising the chances of issues for unborn children and children born with birth defects. Again, the stress and worry associated with this would be huge. Emotional as well as monetary cost.

Q11. This would be great, thinking of my own daughter and the help it would give her when she would come to that age. They would not feel then as if they are being victimised.

Q12. Think if all pregnancies resulted in women with PKU having children with neurological damage. These costs would be from birth right through to adulthood. Suely these costs should be included as they would be significant.

Q13. I would love these people to put themselves in the life of a child growing up with PKU. Especially in todays world, I constantly worry about bullying because my daughter is different, about her rebelling and eating whatever she wants.

Respondent 99

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. The dietary choices and lifestyle implications afforded through the provision of Kuvan should not be restricted by the age of the individual. Secondary neurological difficulties associated with poor dietary control or lack of dietary choice should mean that ALL people with Pku regardless of age should have right of access to treatment. This issue extends beyond normal physical development. High phe levels effect cognition and emotional well being in all age groups.Anything which can assist to mitigate these consequences must be available to all ages.

Q3. I do not agree with NICE's view

Q4. I have worked in adult mental health for 25 years and have seen the effects of depression and associated cognitive difficulties many times. My daughter,who is now 15 years old has suffered from depression associated with her Pku diagnosis and subsequent impact on her self concept.I do not want a lifetime of depression for my child.Any available treatment for this condition must be available for adults. Anyone having to adhere to this diet on a daily basis for a lifetime would agree. Research indicates that uncontrolled phe levels continue to damage the brain.Would you treat someone with diabetes until the age of 18 and then stop??

Q5. I agree with these statements. I have had to work part time since my daughters diagnosis. I have missed out on opportunities for promotion because of the need to be at home more often to monitor my daughter’s dietary intake.I have had to fight to retain my part time status as my employer does not fully understand the implications of loss of dietary control.Education around Pku is greatly needed.

Q6. I work in the health service,I have worked part time because of my daughter’s condition. Greater dietary choice and assisted control would mean I could increase my hours and ‘give back’ to the health service.

Q7. I totally agree with NIC’S comments. This condition has damaged the lives of so many people and their families.Direct health consequences of the diagnosis and dietary control difficulties is a lifelong burden.We have a moral responsibility to advocate for anything which can release patients from this suffering.

Q8. There is no opportunity for spontaneity in life for Pku patients and their families. Everthing has to be planned.Social interaction and attendance at parties in childhood becomes massively stressful. The potential for bullying in childhood and adolescence is always a fear. Lack of opportunity to fully engage in sporting activities or to realise their full athletic potential because of Pku is another issue for young people. Damage to self concept and core belief systems is ongoing. Family planning and health in pregnancy is a critical issue for both mother and developing fetus.There are no days off with this condition for patient or carer. Anyone having to follow the diet for even one day would understand what it means. NICE must support these patients.

Q9. Calculation of dietary exchanges requires a level of intellectual ability. Managing impulses to eat foods could be difficult for people with learning difficulties. Support and access to services is critical for people with Pku,outreach services may be required to prevent dietary mismanagement in the travelling community

Q10. Research ,which is widely available on this subject ,confirms the damaging impact on the development of the fetus by high phe levels.This condition was first identified in the 1960s,there is no excuse for refusal to acknowledge the clinical evidence available 60 years on.

Q11. See above

Q12. Poor dietary control in pregnancy has long term cost implications .Prevention of damage to the unborn child must be considered to offset the financial consequences of this.

Q13. Provision of this drug to Pku patients is a moral and human right.If you’re not part of the solution you’re part of the problem.

Respondent 100

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I think it's immoral and totally disgusting to expect an 18 year old to switch from a normal diet to a PKU diet which is highly restricted. It's just not reasonable. The affects will be severe mental health issues when the child comes onto the PKU diet and I'm absolutely certain that hardly anyone would be able to go from freedom to restriction surrounding food without developing an eating disorder, (like my sister who has PKU). I've watched my sister dealing with restriction on the PKU diet and then developing Anorexia and Bulimia. I've also watched her struggle with depression and anxiety when she's been unable to stick to the PKU diet for a couple of days because her phenylalanine levels have got to high. How can you even consider making 18 year olds go through this trauma at a pivotal time in their life, when they're taking their first steps into adulthood? At 18 many of them will be going to uni and are in control of their own diets for the first time. They will then be at university or navigating life without their parents watchful eye, having to buy PKU friendly groceries which are far more expensive than normal groceries. I know when I was a student - I had no money. But I was able to buy cheap food like cheese, normal bread, noodles. PKU sufferers can't do that. Please do not do this to suffers of PKU.

The fall out of this (mental health, eating disorders, brain damage) will cost the NHS FAR more than offering Kuvan for a patients lifetime.

Q3. I do not agree with NICE's view; NICE's statements are contradictory

Q4. Through the PKU community I have met adult suffers who came off diet as adults and now have long term mental health and brain damage issues.

Q5. Growing up with a sister who had a highly restrictive PKU diet, I was surrounded by stress constantly as a child. Watching my sister cry because she couldn't eat certain foods and having to have 'weird' lunches at school, when her friends could eat school meals. The words 'diet' and 'restricted' were always used in my household. From the age of 5 I was checking the protein and calorie content on food. I watched my

sister go through an eating disorder, and I developed one myself because an obsession over restricting food had always HAD to be present in my household. My parents did their best and were amazing, but I've seen my mum cry from stress because she's having to constantly try to find food that is edible for ****. My mum always had to cook two dinners - one for us and one for **** (my PKU sister). I used to hide non PKU friendly snacks and eat them in my room alone so I didn't make **** feel bad for not being able to eat nice food. I've watched **** throw caution to the wind a couple of times and start eating fairly normally and then spiral into depression caused by excessive levels of Phe in her blood. She and our entire family would welcome a less restricted diet. It would change our lives.

Q6. Yes, because buying groceries for families with PKU members is a different ball game and is a LOT more expensive.

Q7. My sister's Phe levels have caused her to develop Anorexia, Bulimia Depression and Anxiety over the course of her lifetime. She also gets frequent migraines if her Phe levels are too high. It's been traumatic watching her go through this. It's not just children with PKU, it's adults with PKU too. That's what NICE need to take into account.

Q8. Yes - **** should be having counselling due to her long term mental health issues which have been a by product of her PKU diagnosis and Phe levels. She needed extra support in school regarding food. She has also had counselling for her Anorexia. These are all added costs. They are needed and necessary.

Q9. No, NICE has not considered treating people fairly because they have not taken into account adults living in poor income areas and in low income families who cannot afford the variety in food to make a PKU diet doable. If all you can eat in the way of veg is the basic cheap stuff, then how easy is it going to be to stick to diet? If you haven't got the knowledge or come from a background of making nutritious food then it will be very difficult to start doing so as an adult.

Q10. Kuvan to assist in the conception and pregnancy for PKU mothers.

Q11. Not at this time.

Q12. Cost of additional groceries to sustain themselves if they don want to give birth to healthy children and remain healthy throughout their pregnancy whilst eating a fair, varied and nutritious diet will be great.

Q13. It is disgusting to suggest that PKU sufferers over the age of 18 will not receive treatment. I have never heard such an unfair and ludicrous statement. This would not be allowed if it was a less rare disease such as diabetes. Do NOT do this to sufferers of PKU. It is totally immoral and unforgivable.

Respondent 101

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I feel this would be extremely detrimental to mental and physical health of every single child asked to do this. I find the suggestion absolutely disgraceful, to expect a child to have the freedom to eat a wide variety of food and then take it away from them is cruel.

Q3. NICE's statements are contradictory;Clearly NICE statements are contradictory as people are deemed adults at aged 18, so from 18-25 they are at risk of long term brain damage

Q4. I would nice to study the Nspku guidance and response to this

Q5. I completely agree with all of this. I have four children with pku and since my 1st child was diagnosed 7 yrs ago the mental load of the diagnosis has only got heavier. I get brief respite when 2 of the children attend school but with that comes extra preparation and organisation each morning as well as lots of complex reconfiguring after school as I figure out what and how much of the food provided was actually eaten and recalculate what the protein allowance each child has left for the day. It never leaves my mind, and the worry and stress only gets worse as the children get older and want/need independance and become more aware of how they are different and how that affects their relationship with their peers.

Q6. Yes as pku has such an impact on the whole family and wiser family circle. I have had to give up my full time job and no longer work. I was employed with Surestart working with vunerable familes and loved my job but could not continue as the workload with pku was too much. I am now surviving on tax credits which doesn’t sit comfortably with me but I have no other choice.

Q7. I agree with this statement and would also add they have problems sleeping and their dental health also suffers due to the high sugar protein substitutes they have to consume 3/4 times per day

Q8. My children receive extra support at school and with their metabolic team, thankfully we have not had to access social services support but this is only because I have managed to keep my mental health under control which is not easy. Pku massively affect our families quality of life and this needs further investigation

Q9. Everyone should have access to Kuvan regardless of their background. The condition is multifaceted and it is so much more than just a diet, it is a way of life that no one would choose to follow. It is extremely complex and I find it is very difficult to follow and I am qualified teacher caring for my 4 children who have the condition. It would be practically impossible for an adult to follow if they had come off diet prior to taking kuvan and also for any of the groups mentioned above.

Q10. NICE clearly have not researched this area enough as there is lots of evidence to contradict and prove this statement is completely inaccurate.

Q11. I cannot speak personally on this as I do not have pku but I have a daughter with pku and would hope that her health and that of her unborn children would be paramount when the time comes. And kuvan must certainly play a role in this.

Q12. I find this a massive oversight and demand they calculate these costs and include them.

Q13. I feel there are gaping holes in the research and evidence that NICE has considered and suggestion made are totally ludicrous. Hopefully the responses received will emphasis this and the pku community will get access to Kuvan like the majority of developed countries as soon as possible.

Respondent 102

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I consider it unfair and cruel to expect PKU patients to suddenly have to stop KUVAN at the age of 18 and expected to revert back to extremely strict and restricting diet and conditions.

Q3. NICE's statements are contradictory;KUVAN should be accessible life long as PKU can affect the brain and living conditions life long

Q4. N/A

Q5. We would welcome any treatment that improves the life of our son, even if that may be just an exchange or two a day (one exchange = 1 gram of protein) as this would still be life changing. As a family we avoid eating out publicly, attending childrens parties, and even find that family and friends, in their own words, are "scared and daunted" by PKU and how to look after and manage it in our absence even though there is nothing they wouldn't do for him. Starting School, making friends, going to events, planning days out are all that more difficult and stressful with PKU. It is distressful and upsetting at times and especially when you have your son asking why he cant be "like his friends", why he can't eat the same as them, why he has to have supplements. The effect of PKU on children/adults with PKU and their friends and family can not be underestimated.

Q6. *[no response given to this question]*

Q7. I agree with NICE's statement and I see a difference in my son when his levels fluctuate.

Q8. *[no response given to this question]*

Q9. I don't feel like the proposal treats people fairly

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. As a parent this is an extremely welcomed development in the fight for KUVAN and potentially life changing for our son if he is a responder. My concerns at this point are of course that he doesn't respond at all, but more that there are enough opportunities and chances to look for a response rather then being written off immediately, having heard stories that not everyone responded to the first trial but responded to the second.
I am also concerned about the recommendation of only 10mg being prescribed after hearing that some didn't respond to 10mg but responded to 20mg where some respond to as little as 5mg, some flexibility on dose would be important.
The worry that he could respond and then have the drug taken away suddenly at 18 is a major concern for us, this would not only be unfair but it would also be cruel and would significantly affect his quality of life.
Please do not underestimate the value of such a life changing drug as Kuvan to PKU patients, of all ages, and their families and please recognise this is a LIFE LONG CONDITION.

Respondent 103

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I have three young daughters with PKU and I am very concerned that if they were to access Kuvan and then to have it removed the effect of this on them would be horrific. It would be mentally torturing to have been able to avail of some normal foods only to then stop eating them. The idea that they could engage more socially around food and eating out in restaurants and then have to stop this as their brains do not stop developing at 18 years of age. Throughout the last 13 years I have had to watch my children struggle at social events and parties and even family events as they could not partake as no suitable food was available. To watch that happen to my 18 year old daughters is a completely unethical situation.

Q3. I do not agree with NICE's view

Q4. Medical history of PKU provides much medial evidence of the falsehood of the above statement in question 3.

Q5. I welcome the chance for my children to avail of Kuvan. I am devastated that it would not be a long term treatment for my children. The treatment would be removed at 18 years. The treatment proposal by NICE is very bittersweet.

Q6. The daily struggle within a PKU family is huge. I have had to reduce my job to part time to care for my children with PKU. It is a second job ensuring all foods and medical supple drinks are in the house, I can never run out of PKU food as then I cannot feed my children. The burden of stress on continuing to ensure required blood levels remain within limits and helping children cope with high blood levels and the effect of this on the child.

Q7. Yes i completely agree with this.

Q8. My children with PKU have struggled at times with school work and sports. This is generally due the high blood levels or the issues identified of focus and headaches.

Q9. PKU is a lifelong condition, treatment should be offered lifelong.

Q10. My three daughters will require Kuvan to have healthy children. this is unacceptable option not to have it available. The risks to the unborn child are huge.

Q11. PKU is extremely dangerous for the unborn child with OKU mother.

Q12. I would like to see this reversed.

Q13. This is hugely disappointing proposal from NICE , I wish to see Kuvan extended for use by adults.

Respondent 104

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. As I've stated above, the PKU diet id and incredibly intricate and difficult diet to get to grips with. Rules on what does and doesn't have protein in changes every single day so to expect a young adult to be on top of all that is very unrealistic. I developed anorexia and bulimia at the age of 16 and I'm still recovering. I had no inclination to follow the diet and didn't handle my diet therapy at all. I got to the point where I was nearly hospitalised because I had lost so much weight but also my blood phe levels were out of control. eating disorders in PKU are very common, especially in young people and adults who completely disassociate with PKU. I think forcing a person to stop taking a life changing drug at the hardest time of development is unfair and will be detrimental to their health. I developed these struggles knowing how to treat my PKU diet, so I can imagine the shock of restricting food to such a high extent so quickly will see a rapid deterioration in someones attitude toward food.

Q3. I do not agree with NICE's view;NICE's statements are contradictory;NICE have failed to realise that the fall out of not conforming to the PKU diet is white matter damage, no matter what age. I struggle with concentration if a go over my protein balance on just one day. I can't drive and I can't write very easily. It's like having to work through a massive fog, my brain and thoughts feel heavy and I would say I am generally pretty good at following my diet. Adults have a lot of responsibilities and with PKU everything is made harder to do. Kuvan could help so many adults with brain function and NICE have recognised that then contradicted that. It's hard for me to even focus on writing this response form. The slightest fluctuation in phe makes everything harder and NICe have not accepted this.

Q4. I used to have a great memory when my mum was in charge of my diet but as I've got older, my ability to concentrate and my memory has got worse. I feel fatigue at about midday and have to drag my brain through the rest of the day, I need help and Kuvan could provide that help to me and so many others.

Q5. My mother and father have had to educate medical professionals on my diet all my life. The treatment for me has always faltered because people know nothing about PKU. When I had appendicitis I was left untreated for two days because the surgeons were worried about anaesthesia's effect on me. My parents had to assure them it would not effect me whilst I was in agony for days being left untreated. The reality of PKU infiltrates all aspects of my life. In school everyone use to get cakes on birthdays and I was sat watching everyone eat. My parents had provided alternative snacks yet my teachers were too scared to give me them. The lack of knowledge about PKU is exhausting for PKU sufferers and carers the same lack of understanding has happened again here, meaning carers and PKU sufferers have to draw on traumatic experiences because of NICE's ineptitude to understand the true impact of PKU on relationships and life in general.

Q6. My family members have gone without foods they would have wanted to eat because I can't be trusted to follow my diet. We have had to adapt holidays, room space, fridge space just so I could follow my diet therapy properly.

Q7. I have both bulimia and anorexia because of my poor relationship with food which is a direct result of PKU. I feel tired all the time and am doing an extremely physical degree at university which means I have to work twice as hard to get through the day compared to the rest of my cohort. Treatment like Kuvan would make my life so much easier and every day would be enjoyable and not a struggle.

Q8. My quality of life would be massively improved if Kuvan was accessible. I have been bullied for my PKU, I have gone days without eating because of my PKU in conjunction with my anorexia. I have had failed relationships because of PKU and have had strained relationships due to arguing over the management of my diet. I get fatigue every day and brain fog every day even when I stick to my diet. I have had to take time off school to attend therapy for my eating disorder as well as attend clinic for PKU. I have missed out on school trips and holidays because of it. I have even been refused some treatments because of doctors not knowing much about PKU. I would say there's a pretty large impact on quality of life and if people took the time to actually communicate with the PKU community they would get to understand how PkU effects every choice we make. Many PKU sufferers have a lot of trauma that they are having to relive every time NICE gets this decision wrong and that trauma will never go away, but with Kuvan at least the quality of life will be improved and relationships with family will be improved.

Q9. I have polycystic ovaries and suspected endometriosis. This is paired with the fact that pregnant PKU sufferers have to follow a highly restrictive diet both before and during pregnancy. It could take me many years to get pregnant, if I can at all, and that would mean living off of essentially salad leave for years. The decision NICE has made is discriminatory and unfair. No one should have to feel like they can't have a child because of a medical condition that has the potential to be cured and the drug that could cure it is being denied.

Q10. NICE should acknowledge both the physical and mental toll pregnancy can take on a woman with PKU, who is totally responsible for the health of her child and herself. If the diet therapy is not followed severely, the child will be very physically and mentally ill. Kuvan would make it easier for women to go through pregnancy and nourish her unborn child properly.

Q11. Not offering Kuvan to mothers with PKU is a huge ethical issue. This could mean the potential to save both a mother and child from physical and mental deterioration and disability.

Q12. NICE have only looked at short term costs of PKU. They haven't considered that white matter damage causes dementia, which will only be seen late in a PKU sufferers life. They have excluded women from their costs and the costs of caring for a disabled child if maternal PKU is not followed properly.

Q13. NICE's decision poses multiple ethical and moral issues. It is discriminatory to PKU adults and especially women. It has meant PKU sufferers have yet again had to share traumatic stories of a lack of understanding for PKU. I have been fighting for this drug all my life and I will not stop until I get it. PKU patients aren't an economic entity, we are human beings with lives, families and responsibilities. NICE needs to ask themselves how they will respond in the future when those children who have had Kuvan taken from them develop mental health issues and

mobility issues. Read the evidence that the PKU community is giving you, it is all there in black and white. PKU sufferers are traumatised and tired as all their lives they've been given incorrect treatment or even been told they could come off diet when that decision was found to be detrimental to their health. We are tired of paying the price for a lack of understanding and ignorance about how this condition should be treated. Make the right decision.

Respondent 105

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. it would be extremely difficult and very unfair to expect a patient to have use of Kuvan and then be told at the age of 18 that the treatment was to stop.
Damaging in the fact that the return to the diet would be extremely difficult. Also the mental health issues would be significant.

Q3. I do not agree with NICE's view

Q4. Patients who have in the past come off the diet have experienced "brain fog", serious mood swings, depression, anxiety and a host of other mental health issues.

Q5. Dealing with the daily needs of a child with PKU is time consuming and a challenge. each meal/outing/holiday has to be carefully planned and nothing left to chance. The long term affects of poor dietary management are ofter forgotten about. 'DIETARY management is both a full time job and a very serious responsibility.
of course it a treatment that allows a less strict diet would be most welcome

Q6. ABSOLUTELY!!
The entire family is very much impacted with a PKU child

Q7. The diet needs to be strictly controlled and kept well within the guidelines

Q8. This needs to be addressed. information collected to help with patients in the future.

Q9. NICE have not properly concluded

Q10. I think all women should be offered KUVAN whilst trying to conceive and during pregnancy

Q11. I think KUVAN would greatly help in this category

Q12. perhaps this should be costed against the cost of KUVAN,

Q13. I think the idea of stopping treatment at the age of 18 is ludicrous!! The draft in areas lacks evidence of having done any proper research into PKU, both living with it and the side affects of coming off diet.

Respondent 106

Q1. I agree completely with this recommendation

Q2. The isnt a cute for this condition...and why should the treatment stop why they reach 18 I have 2 children with pku 8 and 4

Q3. I do not agree with NICE's view

Q4. Nothing further to add

Q5. Yes I agree

Q6. Absolutely

Q7. My eldest has adhd

Q8. Nothing further to add

Q9. No

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 107

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Kuvan should not be stopped at 18yrs

Q3. I do not agree with NICE's view

Q4. No

Q5. Yes I totally agree

Q6. Yes

Q7. Yes

Q8. *[no response given to this question]*

Q9. No. It needs to be given to all

Q10. It's should be given to all ages never stop this treatment

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 108

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Never heard of a drug been taken away from children when they reach 18. Children will have become used to 'normal' food and their palate will not have developed to their prescription foods. Which may not sound like a huge issue, but as a parent of a child with PKU I have tried low protein prescription pastas and breads and couldnt imagine eating them daily, especially when I know what they should taste like. Organising my daughters food for the day actually uses a lot of maths, food scales and I use a calculator several times a day to make sure I do not give her too much protein. It would be neglectful to expect an 18 year old to switch to new foods, never eat some.of their favourites again and place this burden of calculations on them without the gradual learning how to manage their food and keep track. Most teenagers I know would find it hard to never have any of their previous foods again which would be the situation for many PKU sufferers as they are too high in protein. Even foods like sweetcorn, broccoli, potato and cauliflower gave to be stringently measured. Can you imagine being a teenager out with your friends and having to scrape sweetcorn off your meal to weight it (with food scales you have to bring everywhere) then move on to the next ingredient and the next to know your consumption to safe guard yourself from brain damage?

Q3. I do not agree with NICE's view

Q4. *[no response given to this question]*

Q5. 100% agree about the time stress, constant worry that families of PKU sufferers have. I worry about my little girl reaching her milestones every day and brain damage is a constant worry. I have to explain her condition with nearly all professionals I come in to contact with GPs, dentists, health visitors, doctors in A&E... I have had to educate staff at both nurseries my child has attended and keep them updated regularly each time she is prescribed more.protein supplement.

Q6. Yes I changed my working pattern from fulltime to part time to cater for my daughters needs.

Q7. My daughter is a constant worry for us and has always been late on meeting her milestones and is under review by specialist paediatrician for suspected global delay that I whole heartedly link to her PKU. In this time should parents have these worries of their teen or adult child having high phe levels, a glance at the side effects of high phe speaks for itself.

Q8. *[no response given to this question]*

Q9. My daughter is 3 and we worry that she may never overcome her learning difficulties as she is very different to her peers and has been referred to professionals for review. If she were to be diagnosed with a learning disability I do therefore think it would be imperative that she would be entitled to a drug beyond 18 that can save guard her hurting her own brain.

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. Unethical to allow a child to grow and develop on a drug and then snatch it away when they reach adulthood leaving them unprepared for looking after themselves.

Respondent 109

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I believe it is cruel to allow a child the benefit of a less restrictive diet and then take this freedom away from them when they turn 18. In my opinion this will lead to people turning 18 being unable to adapt to the restrictions and not being able to adhere to the diet which will be detrimental to their health and life outcomes.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. I know a late diagnosed adult sufferer of pku who needs a full time carer as a result of the brain damage and cannot live independently. Two of my first cousins with pku suffer debilitating anxiety and depression and poor executive functioning making work and study difficult as a result of their pku.

Q5. Management of my child with pku's diet is complicated, time consuming and stressful. I have considered reducing my work hours to dedicate more time to cooking and planning his meals. Family occasions and celebrations are particularly difficult and I believe my child misses out on

social invitations because others are fearful of providing food. This is upsetting for me as a parent as well as for my child who feels excluded and iaolated.

Q6. Yes. Management of pku impacts the whole family. A holistic view of the impact on the individual and their family is more appropriate.

Q7. The mental health and wellbeing aspects are of critical importance. These symptoms are debilitating and harm the life outcomes of people with pku. Such symptoms are preventable with better management such as through kuvan. It is unfair to accept dietary treatment alone when this is known to have suboptimal outcomes. I have seen first hand the terrible toll depression, anxiety and other cog itive difficulties have had on my cousins with pku. This has cost them employment, relationships and resulted in very real suffering.

Q8. There is unquestionably a cost to the nhs associated with treatment of depression and anxiety related to pku. Further to this there is a cost to the state from disability benefits or universal credit for those unable to work or unable to maintain employment as a reault of pku. There is a cost to the department for education feom suplort needed for chilsren in school with special educational needs like adhd associated with pku. These are facts. My two cousins living with pku have needwd all of these extra types of support over their lives and are still in need of these services. Their lives would have been improved, their educatuonal outcomes and their opportunities would have been better had they had access to kuvan and the cost to the state of their care and to the taxpayer would have been much lower.

Q9. Nice has not properly considered the many groups for whom management of pku is more difficult, and that in failing to consider this it is making things even more difficult for those belonging to these groups.

Q10. I believe nice should recommend the use of kuvan for the management of maternal pku. There is evidence high phe levels are damaging to unborn children. Kuvan is effective in lowering phe levels and this means it is a valuable tool to manage pku.

Q11. My female cousin with pku is too afraid of the impact on her baby of her high phe levels and has resigned herself to the idea she will never be a mother. This is heartbreaking for her. She believes she would not succeed in keeping her phe levels in the safe range and that as a result of this, she must never have a child. To forgo the opportunity to become a mother is a grave sacrifice and one which she would not have to endure if kuvan were available to her.

Q12. This seem like a glaring oversight. The costs associated with the lifelong care of neurological damage in the children of pku mothers should be considered and the cost saving from avoiding such damage is highly relevant.

Q13. The current dietary treatment for pku results in suboptimal outcomes. Nice acknowledges that kuvan has improved outcomes and this should be extended to benefit people living with pku for their whole lives. They do not grow out of pku, their health and mental wellbeing matters their whole life, not just when they are under 18.

Respondent 110

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I’m unsure how a teenager who has lived on the relaxed diet that Kuvan can offer is to be expected to be able to learn and manage a much more complex diet at a time in their lives when they are just taking the first steps into adult hood. To have to get used to supplements and unpalatable foods would take great willpower and would almost certainly undo all of the work that has been done reinforcing the current message of ‘PKU diet for life’ there will be very few 18yr olds able to (and willing to) go back to the PKU life. This in turn will produce many, many adults struggling with the side effects of a high protein diet. Brain fog, poor concentration, anxiety, depression to name a few. The effects of which are shown across all facets of their lives. It will put more pressure on already stretched mental health teams. Taking the drug away at 18 could be potentially devastating to so many.

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. I agree that PKU can put a massive strain on a family. My relationship with my son suffers because as he gets older he with argue with me about taking his supplements and controlling his phe levels. We are arguing over things that could be avoided. My household stress levels could be greatly reduced should my son be a responder to Kuvan!

Q6. Every single person in my close family. Sisters, brothers, grandparents, aunts and uncles, have cared for my son and his PKU. Without this help our lives would be unmanageable. Any time we were in hospital (I had breast cancer when my son was young), someone had to care for my son and we had to give them the knowledge and trust that it takes to care for someone so vulnerable.

Q7. I agree entirely. In fact I am glad to hear that they have acknowledged the side effects that we have seen as a family when our son has levels that are out of range. My son also has epilepsy and these effects can cause his epilepsy to worsen. If he doesn’t sleep well or is acting wreckless it can have a huge knock on effect.

Q8. *[no response given to this question]*

Q9. The cost effectiveness of Kuvan become clear when you offset it with the cost of supplements, prescription foods, extra hospital appointments and the extra monitoring needed for pregnancies. The cost of all clinic appointments and staff needed to treat PKU. More so when a person is struggling with it. Add the potential cost of mental health services for the adults who were using Kuvan as children and are now living with the negative affects of living off diet or struggling to stick to the strict new regimen. It all adds up to a huge cost over a lifetime.

Q10. The fact there is no evidence to consider in testament to the willpower and strength of these ladies with PKU. They are constantly taught from a very young age about contraception and the difficulties they would face if they did not control their pku while pregnant. NICE should wholeheartedly recommend KUVAN during pregnancy.

Q11. *[no response given to this question]*

Q12. This needs to be taken into consideration because if they remove Kuvan at 18 there are going to be many women struggling to control the strictest form of a pku diet while pregnant. The risk of more children being born with brain damage is incredibly real!

Q13. Please listen and take on board all of the evidence that has been presented to you from the PKU community. We live and deal with PKU daily. As a parent it scares me greatly that my son could be expected to go from a relaxed diet to a strict one during a time in his life when she should be taking his first steps into university or a work place. The side effects of high phe levels have the potential to affect the rest of his life, his career and his family. Please take this into consideration when making your recommendation.

Respondent 111

Q1. I think kids and adults should be allowed it.

Q2. I don't agree with it getting stopped at 18, they should be allowed it into the adult years too.

Q3. I agree with NICE's view that there is no risk of long term brain damage in people with PKU aged over 18

Q4. *[no response given to this question]*

Q5. I agree

Q6. I think it should be through NHS for families that don't have alot of money.

Q7. I agree. My daughter is 6 and says she wants to die when she's having a bad day.

Q8. Should be free on NHS. For struggling families.

Q9. *[no response given to this question]*

Q10. Agree

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 112

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. That’s a cruel suggestion. I can’t imagine how much damage that would do to them mentally.

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. It would be great to have a less strict diet for my son. It takes up soo much time bc and is so stressful. however it is really important that this is offered for life. Pku is life long and the diet needs to continue for life. It would be terribly unfair to give young people a sense of normality only to tear it away at 18.

Q6. Yes. It’s meant a lot more stress. It means less work and more caring. It means a lot less outings. And has an impact on the economy.

Q7. Yes. Our 10 year old son can be an emotional wreck at times. Reducing these symptoms would be brilliant.

Q8. *[no response given to this question]*

Q9. *[no response given to this question]*

Q10. Maternal PKu should be top priority

Q11. I’d make pregnant women the first priority here. Their diet has to be so strict and it must be exceptionally difficult with pregnancy cravings etc.

Q12. These costs could be significant for families, the nhs and the state, this should be a priority.

Q13. *[no response given to this question]*

Respondent 113

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. As a mother who raised two boys with PKU, the teenage years especially the later ones were the most challenging and they’d been on diet since birth. This is a ridiculous and dangerous idea.

Q3. NICE's statements are contradictory;That is not what we have consistently been told

Q4. *[no response given to this question]*

Q5. I totally agree. Children with PKU are singled out and unable to join in so much because we base all our social interactions around food or involve food: birthdays, Easter, Christmas, picnics, sleep-overs, dining out, etc

Q6. Yes absolutely

Q7. My entire life when my boys were young was about their Phe levels we loved it 24/7. I even learnt the American way of treating PKU to give them the best options. I cooked relentlessly and their Phe levels were solid. We didn't experience any of the above related to Phe levels. But I was lucky we could afford for me to do that

Q8. What a complete and utter failure that none of this has been addressed before. My boys are now 34 and 31 and planning families of their own. You've had a lot of years to sort this out

Q9. No!

Q10. Stop thinking about £ bring drug companies to heal and start thinking about human lives

Q11. N/A

Q12. Why is their PKU uncontrolled?

Q13. A drug is available to bring a normality of life and here we are looking at 'the cost' sometimes I just despair

Respondent 114

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. A difficult age to expect PKU children to suddenly adhere to a complex dietary regime they have not had to follow, and particularly in the absence of evidence about the best course at that time.

Q3. I do not agree with NICE's view

Q4. My family friend whom I have accompanied to specialist appointments in recent years is now 62 with learning difficulties, COPD, MI, arthritis, and depression was regarded as a severe case in childhood and not allowed to carry a pregnancy through for risk of fits.

Q5. Indeed, my friend had to eat a ghastly 'gloop' as a child and now really eats rather poorly. She was adopted and the attention she needed as a child made her elder adopted 'sister' rather resentful such that they have had little contact since their mother died. Moreover the elder sister has recently died of Covid at 69. There is no doubt that medication during her life which would have allowed her to eat more normally would have had great benefits.

Q6. Indeed. See above response.

Q7. As listed above. My friend exemplifies exactly the multiple comorbidity recognised in PKU.

Q8. My friend can remember her mother being told she would never be able to read! She was the first child diagnosed in Stoke at the age of 4. She has only ever had incidental employment, was a carer for her late mother with dementia and late husband with PVD. Would have liked to be a nurse if she had been able to achieve qualifications. She survived on benefits; I persuaded her to be referred back for regular specialist review so she would have all medical support for today's DLA equivalent.

Q9. If my friend had been able to take medication all her life she would have achieved greater independence and much better socio-economic situation with far less comorbidity I suspect.

Q10. There needs to be good research for currently unknown benefits.

Q11. If Kuvan had been available many years ago my friend would have been able to carry a pregnancy and achieve qualifications in life enabling good employment.

Q12. See above. I have no doubt my friend would have experienced less learning difficulties if she had received Kuvan as a child and probably subsequently.

Q13. There should be open acknowledgement of what is as yet unknown with positive recommendation for research. The long available European recommendations should at least be achieved in UK.

Respondent 115

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. You can not expose someone to a life which they will not maintain and keep forever, giving them a life of privilege and more normality to then take it away, it is unfair and inhumane.

Q3. I agree with NICE's view that there is no risk of long term brain damage in people with PKU aged over 18

Q4. *[no response given to this question]*

Q5. Yes I agree completely.

Q6. Yes, my personal experience with my little brother who has PKU, this would change his life, I genuinely believe that he would become a better person in himself and he would massively benefit within himself mentally and physically with this medication.

Q7. Yes I agree, as said before my little brother at a young age of just 7 years old I can already notice struggles which he may face and obtain from just his actions and emotions at the moment and how he struggles to control his emotions and mental state, therefore anything in order to allow

him to eat more food, gain more energy, feel better in himself, get more protein would be incredible and I think would have the best impact on his and my families life for the better.

Q8. *[no response given to this question]*

Q9. *[no response given to this question]*

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 116

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. My friend has a young child with PKU. I was staggered to hear about how this drug could be taken away from this child when he turns 18. From what I have heard and learned about this condition, this would completely turn a teenagers life upside down. They will be used to eating a relaxed diet and suddenly, in my friend's child case, have to revert to learn a diet of 5g of protein a day. Whilst doing his exams, going to uni and all other stuff that happens when you turn 18. I think this is beyond cruel. Teenagers find it hard to learn how to cook normal food anyway when they turn 18. At this point NICE are saying they have to learn how to bake PKU bread, navigate the prescription ordering system and many many more activities.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. I have already seen the impact upon my friends life. He has had to take a part-time job in order to have the time to manage his sons diet, as well as to avoid the child going to nursery more than a couple of mornings a week, where mistakes in the diet outside of the control of the parents can have awful consequences such as brain damage and learning difficulties. The burden on carers of children with PKU sounds huge given that every meal and drink has the weight of the thought of if you are essentially poisoning your own child.

Q6. Yes as per my earlier answer, society is losing out from my friend going part time and paying less tax into the system as a result.

Q7. My friend's child is very young and from what I hear his PKU is being managed well at the moment but as the child becomes more independent, I can only see this becoming more difficult and the onset of those symptoms you have described here.

Q8. *[no response given to this question]*

Q9. NICE haven't considered any of these aspects. They show no understanding of what life with PKU entails.

Q10. This is astonishing. Surely the costs of a child born with defects as a result of uncontrolled Phe levels during pregnancy will be SOOOOOO much higher than the costs of giving the drug? So short-sighted.

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. I want to make a comment about the dosage. 10mg/kg - the maximum capped dosage. What a sneaky decision. Other countries routinely prescribe 20mg/kg. The consultation states that in US, the average is around 20mg and in Europe around 13mg. The NICE appraisers need to revisit GCSE Maths and learn the difference between an average and a maximum. Clinicians need the flexibility to prescribe as they see fit within the manufacturers guidelines. Some children may need 20mg, some may respond to 5mg or 10mg. NICE are setting many children up to fail.

Respondent 117

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. My nephew has a young child with PKU. I heard the news that Kuvan would be withdrawn from a patient at 18 years old and was staggered by this news. At 18 years old, my nephew's child (******) might be taking his A-Level exams, preparing to go to university or work, possibily about to live independently, and loads of other activities and moments of life that becoming an 18 year old involves. At this point, he will be snapped off this drug and told to revert to a diet where he has to know how to get access to, calculate and cook a diet of just 5g of protein a day. This is unethical beyond words, as it would turn ******'s life (and anyone else's with PKU on their 18th birthday) upside down as he turns 18.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. I know a little about the impact of PKU on my nephew's life. He has reduced his hours and taken a part-time job in order to cope with the diet management, which McDonald (2016) highlighted in her research as taking an average of 19 hours a week. I know my nephew is scared of sending his child to nursery and giving control of this diet to somebody else where mistakes may happen. I hear from my nephew about the burden of caring for someone with PKU has - to have the mental weight that every meal, snack or drink could give your child brain damage sounds like a heavy weight to carry every day.

Q6. NICE haven't. As mentioned, my nephew has reduced his hours of work significantly. This has an economic cost - he will be paying far less tax into the system as a result.

Q7. ****** is very young and his levels are well controlled at the moment, so he hasn't experienced the symptoms described here, but it sounds like it they are expected to come and a matter of time given he is classical PKU and will have to struggle on just 5g of protein a day.

Q8. *[no response given to this question]*

Q9. NICE has not considered any of these factors at all.

Q10. I am astonished to hear the drug won't be given to pregnant women who have PKU. Surely surely surely the costs of giving this drug outweigh the costs of supporting a child for life born with any defects...

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. The dosage. Capped at 10mg is cutting corners. Many children won't respond. Doctors need the flexibility to prescribe within the manufacturers guidelines. By not allowing the dosage of 20mg, some children will be classed as not responsive. It is like having a headache and saying paracetamol is not an effective drug is just giving 1 tablet - you would then have 1 more! The US average dosage is close to 20mg and in Europe around 12mg, as stated in the consultation. NICE needs to understand GCSE maths and the difference between averages and maximums. Some children may only need the dose of 5mg or 10mg, but some may need 20mg - this will average out at around the European figure, but to cap at 10mg is simply unethical and irresponsible.

Respondent 118

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I think it would be very hard mentally and physically to allow children to have kuvan and then stop it at 18years old..They would have to readjust to a new way of living that they wouldn't understand!

Q3. I do not agree with NICE's view

Q4. No

Q5. Yes I agree totally.

Q6. Yes all family members need to be aware of the diet and it's consequences if not followed correctly, this will include friends as they get older.

Q7. I agree that they need a treatment that can reduce PKU symptoms.

Q8. I think more time and money should be put into collecting this information for the families that may need them and that they will have access to the required resources and medical teams. No data means that a full picture is not available therefore families and children are not getting the help and support they should be whereas if you have any other condition support IS available.

Q9. I think all people should be given the support and opportunity to try kuvan no matter what their language disability may be. If the right support and teams were available they would have a greater chance of managing their diet.

Q10. Unless tests are carried out properly they will never no and what mother to be will want to try kuvan or not try it when trying to get pregnant. I think NICE should advise and help expectant mothers as best they can.

Q11. I agree this would be beneficial.

Q12. I think this should be looked at, some women may have other conditions that make PKU Levels uncontrolled.

Q13. *[no response given to this question]*

Respondent 119

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. pku's should have it for life

Q3. I do not agree with NICE's view

Q4. When being told to come off the diet at 16 like many of us pku's we have suffered brain fog, migraines, depression all in adult life

Q5. Yes i agree I have personal experience through this struggles with relationships, life etc

Q6. Yes I do as it impacts everyone around changes daily life. When in teenage years your mind is all over the place and on top of this pku and trying to get your head around that and being independent enough and to learn about if rather than parents doing it . It is hard alot of stress and frustration . Yes I have been there worn the t-shirt and still I'm struggling.

Q7. Yes I had an eating disorder and was poorly with it, I have depression , aniexty and suffer with headaches and migrains

Q8. I have been refused time and time again on having foods and so this has made my levels extremely high it is like a bone ending circle

Q9. No I do not agree nice has considered treating it fairly everyone with oku be it child or adult should be able to have it and give them a chance of a normal life and make them feel better

Q10. Why cant women not have it ?

Q11. It this is safe and can be used I can't see why as it will help

Q12. Why

Q13. To be honest I think everyone should be giving it and the chance to have a normal life and to not be feeling poorly all the time

Respondent 120

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. If a child is given Kuvan then stopped at 18 year of age, it would be almost impossible for them to go onto a low protein diet. The low protein diet consists of foods that don't taste like 'normal' foods (eg: bread, cheese, pasta etc) and also a foul tasting supplement has to be taken along with the low protein foods. It is almost cruel to allow a child to have some access to more palatable foods (while they are on Kuvan) then just at the time they are starting to take control of their diet on their own, make them go onto the extremely restrictive low protein diet (and supplements). The 18 year old would never had been in the situation where they have to have such strict control over their diet before and all of a sudden they are expect to completely change their diet (through no fault or choice of their own) at a time when life can be quite challenging anyway. Any teenager that is 'different' for whatever reason can find it very hard to cope with, so to suddenly take any the 'normality' they have had whilst they were on Kuvan could be quite distressing and difficult. The low protein diet is quite complicated in preparation and cooking - this is a new skill that has to be learnt - which if the child was going away to University or such like, could find it very difficult to deal with on their own and therefore might not keep to the required diet. If the low protein diet was not kept to, this can cause many other health problems - which could be avoided if the child was kept on Kuvan after the age of 18.

Q3. NICE's statements are contradictory

Q4. *[no response given to this question]*

Q5. I fully agree that carers would welcome a treatment that allows a less strict protein restricted diet. It is extremely stressfull on all members of the family, including those who are not the primary care givers (such as non PKU siblings, grandparents etc). It can be very difficult for grand parents who might look after a PKU child on some occasions to be sure they are following the diet correctly (and sometimes they might offer foods which are not allowed on the PKU diet). This means that the primary care giver will have a lot more stress due to educating everyone who is looking after the PKU child and ensuring the care giver are offering appropriate foods or are keeping to the strict regime. This can also be a problem if parents are separated and one parent does not wish to keep to the PKU diet. Things become even more stressful for the family when the PKU child starts to attend school, as they need to educate the school, but also ensure that the PKU diet is adhered to. This can also present problems in classes such as cookery at school as the PKU child cannot participate in the same way as the other children. When the PKU child goes to secondary school this becomes even more difficult for a parent to have control over foods/diet. Many teachers do not wish to understand about the diet and the effects it can have on a PKU child's learning and this again can be extremely stressful for the child and parents. Over the years, I have had a lot of stress due to PKU, from trying to get a toddler to take his supplement and foods and have regular blood tests, while trying to ensure that he doesn't eat foods his is not allowed. At every outing or social occasion different food has to be organised, which can be very difficult if the person organising the occasion is not helpful or the venue being visited doesnt allow you to bring your own food. Any time care was given by another family member/nursery/school, a lot of work is involved to educate the others and ensure they do keep to the strict diet. Schools can be obstructive and this takes a lot of time to deal with.

Q6. Yes, I think NICE should have taken into account the impact of PKU on other family members - especially the main care giver. Quite often the main caregiver will have to give up work or reduce their hours to manage the diet (this would have an effect on the economic model).

Q7. I have seen many of the difficulties listed in my son (PKU) which are connected to high Phe levels. This can be very stressful for the person with PKU as it can be very difficult for them to manage the low protein diet, especially when they are adults at work. Because they are not controlling their diet correctly (due to external pressures) they are experiencing other health issues related to high Phe levels which in turn have an impact on their life/work. The low protein diet can be extremely difficult to deal with in work situations (as well as at home) but the side effects will exacerbate any problems. To have some sort of 'treatment' that could make PKU easier to deal with would then help prevent some of the effects of high Phe levels which in turn would lead to a healthier life.

Q8. My son has had to have extensive extra support in secondary school due to issues relating to PKU. He has also had extra assessments with the metabolic and psychological teams. I think that children with PKU should be routinely assessed as the effect of a PKU diet that is not controlled properly on the brain can be catastrophic. If there is early intervention many issues could be prevented or at least limited.

Q9. PKU is extremely challenging for anyone, but even more so for those in the groups listed. In some groups listed, it may be impossible for them to understand the PKU diet and therefore they will not stick to the diet - causing avoidable long term brain damage. I do not think that NICE have properly considered treating people fairly.

Q10. From what I understand, a PKU woman who does not adhere to the strict low protein diet can cause damage to their unborn child. This is a totally avoidable situation by allowing pregnant women to take Kuvan.

Q11. If a pregnant women or woman of child bearing age was allow to take Kuvan, therefore having more control over their diet and Phe levels, this would mean that there was much less risk to the unborn child. However, if the woman was not allowed Kuvan, and struggled to keep her Phe levels under control, she could subsequently cause harm to her unborn baby. Once the baby is born it would need subsequent extra support from health and social services, along with the mother. This is putting extra stress and costs onto the healthcare and social services, which is avoidable if the mother has well controlled Phe levels due to the use of Kuvan.

Q12. The costs of neurological damage to the children could be avoided if the mother is supported by the use of Kuvan. I am sure that the costs of Kuvan are much less than the costs of supporting the child throughout their life.

Q13. There are many other conditions that require a controlled diet along with medication (such as diabetes). However, it seems that PKU is the ignored condition - it is extremely difficult to deal with both by the person with PKU and their family members. Anyone with PKU does not have

a choice in the matter - they were born with a faulty gene, but with Kuvan they can lead more of a normal life. Side effects of high Phe levels would be reduced as the Phe levels would be well controlled, therefore, not putting an extra strain on the healthcare system. The cost of Kuvan against the cost of supporting a PKU patient who is not able to control their diet properly (therefore needing extra healthcare support, social support etc) is much less. The ability for a person with PKU to lead a more normal life with Kuvan is priceless.

Respondent 121

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I disagree that they should stop kuvan at 18 alot of people struggle with diet alone.

Q3. I do not agree with NICE's view;NICE's statements are contradictory

Q4. If the people with pku do not stick to supplements and the restricted diet then this can lead to brain damage due to high phe levels

Q5. My son ****** has been struggling for years finding it tough to take his supplements and having a very stricted diet I agree carers would welcome a less restricted diet so I agree totally

Q6. I think nice should have taken into account the impact it has on family members. Because the diet is so restricted and other family members eat different meals to pku it has a very big impact on the person with pku

Q7. I have had experiences of this my son has anxiety carnt focus can be aggressive and its really upsetting to see

Q8. In my opinion it would give better quality of life as they would be able to eat a bit more variety of food

Q9. I do not think nice have treated people with pku fairly as it doesn't really matter if they have disabilities they shouldn't have to be bought into it they should be helped despite there disabilities

Q10. Very high phe can damage a unborn child so pregnant women should be offered kuvan

Q11. They should be given kuvan to help there unborn child

Q12. *[no response given to this question]*

Q13. I'm a mother with child with pku and we have struggled as a family weighing measuring out his amounts of food he can have even found it hard in supermarkets calculating exchanges if he can have it or not . The stress and strains anger and anxiety with him not being able to fit in with his friends I think nice should look at the bigger picture regarding pku

Respondent 122

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. The proposal to allow Kuvan for children is great, but I do not agree that it should just stop when they reach 18 years of age.
My friend’s little boy ***** ***** has PKU and Kuvan would benefit him and his family so much. It would be amazing for ******* to have it, however, it would then be awful for him to suddenly have it taken away at 18 after getting used to a more relaxed diet. To suddenly have to cope with living with and managing the restricted diet as a young adult could be really difficult, and potentially harmful. It’s also the age many go off to university at 18, which is stressful enough anyway and a big life event requiring adjustment. It would be fantastic if ******* and others with PKU did not also have to manage such a restricted diet required without the use of Kuvan.

Q3. NICE's statements are contradictory

Q4. I do not have any experience of this as such but I do question the document and statements made by NICE. They (NICE) advised there is no risk of permanent brain damage after 18, but this is contradicted in other statements where they recognise that permanent harm can occur after 18. So which statement is correct? I would argue that NICE needs to be clearer on this and that the decision to not make Kuvan available after the age of 18 could have extremely harmful and life changing effects.

Q5. Yes I agree.
My friends manage *******’s PKU extremely well, but that in no way means that it has been easy for them. The daily planning and organisation around *******’s food and meals is a lot, and could easily take its toll on a family. Also, not everyone has a strong support network, which could mean they have to fit work around the demands of PKU. A less strict protein-restricted diet would help all PKU sufferers and their families.

Q6. Yes definitely. Like many conditions, PKU affects immediate family members such as parents and siblings, but also the wider family and also friends. Parents will have to meticulously plan and organise their child’s diet and meals, ensure bloods get sent to the hospital etc, and also provide emotional support (as well as their own emotions and stress). Also, friends may offer support by providing PKU friendly food at birthday parties to ensure nobody feels left out (which happens in *******’s case).

Q7. I agree and think this is really important. (No experiences in this respect)

Q8. I’m not sure I understand this statement and question. However, if Kuvan is made available to both children and adults then perhaps the cost associated with supporting families who are struggling with PKU would actually be reduced. Also, if there are people struggling then the costs associated are necessary to support those people.

Q9. It must be extremely difficult for those who have to manage PKU on top of other conditions or learning disabilities. I’m not sure NICE has properly considered treating people fairly, and it all seems to centre around it costing too much. But how can other countries manage to provide Kuvan?

Q10. I’m not sure.

Q11. N/A

Q12. N/A

Q13. Just that I feel strongly that NICE should reconsider stopping Kuvan at age if 18.

Respondent 123

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. We are desperate to be able to give are children the chance to be able to have a more normal lifestyle. It takes all our effort to manage our children's diet and being able to widen there exposure to food would be great however if they were given the opportunity to take kuvan for the next 14 year I don't understand how I could expect them to go back to such and harsh restrictive diet so that they would not experience the severe side effects that come with coming off diet.

Q3. I do not agree with NICE's view

Q4. *[no response given to this question]*

Q5. This is a constant source of stress even down to social gatherings that should be fun for the whole family my husband and I spend children's parties and family gatherings constantly monitoring and preventing family or fiends from offering nearly all food at these gatherings as they are nearly always far too high in protein. There is no spur of the moment, all trips out of the house in regards to food and access to cooking facilities have to be meticulously planned. Even treats that most parents and children would take for granted have to be planed and a whole days menu calculates to allow for this.

Q6. *[no response given to this question]*

Q7. I completely agree with this. My eldest son has suffered from digestive problems since the day he was born screaming in agony, at time ending up with us both in tears. As soon as my children become unwell, as there levels rise you can see them become anxious and there mood become low. It is awful to watch your children become depressed and anxious and not understand why or that it will take time and for there levels to go back to normal and for it to lessen.

Q8. *[no response given to this question]*

Q9. I do not think this is fair treatment. I do not know of any other medication on the NHS that is taken away from a patient once they turn 18! This condition is life long and treated for the patients entire life with blood tests, supplements and vile tasting prescription food as the side effects have a massive impact on the quality of life well beyond 18 years of age.

Q10. At the very least I think any woman who is pregnant should be given this treatment if there is even the Smallest chance that it would help their unborn child!

Q11. At the very least I think any woman who is pregnant should be given this treatment if there is even the Smallest chance that it would help their unborn child!

Q12. *[no response given to this question]*

Q13. Pku patients and their families have waited for so long for the opportunity to receive this medication. Please do not rip away the small amount of hope they have left. Young adults have a lot to contend with normally at 18 years old and ha e so many added pressures and responsibilities. Taking away kuvan at the age of 18 would be heart breaking and immensely difficult for them to Chang. From being treated as a child to then an adult, going from school to a job or higher education and potentially leaving home. Their social groups and standing change, asking a pku patient to then change all other aspect of there lifestyle in regards to diet and the social aspects that go with it after having a greater variety of food available to them just seems cruel. Please reconsider!

Respondent 124

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. I have two young children with PKU. The PKU diet is extremely hard and sinister. It doesn't leave my mind, ever. For my children to try Kuvan, and hopefully respond, would be a dream come true. They would finally be able to enjoy food like every other person does. Birthday parties, bbqs, day trips, holidays!
All of these things, at the moment, are a nightmare for us.
If my children got access to Kuvan, they would grow understanding they can eat freely, and enjoy all these amazing foods and functions and everyday life. Then they reach 18 and it all suddenly is taken away from them?
That really does not sit well with me. This to happen to an 18 year old, when they have just gained some freedom of becoming an adult, making their own decisions, starting university/careers or deciding to travel, and suddenly they must go back to 4 grams of protein per day?! (My children's tolerances)
By stopping Kuvan at 18, would lead to PKU patients to completely come off of their diet, because why shouldn't they? Theyve had all of this freedom with food and now the government have decided they cannot have it?
In addition to this, they WILL then become anxious, depressed, suffer with their mental health (all side effects of high levels phenylalanine in pku patients)... tremors, epilepsy, early onset dementia. What cost will this then have on the NHS? Having to treat all of our children because their medication they NEED to live a normal life, has been taken away.
I do wonder if the people who make these decisions would ever last a day on this diet with these artificial foods and foul supplements, let alone a lifetime.

I ALSO do not agree with this decision because my children arent the first babies to be born with PKU. I have dealt with PKU for 3 years and I wouldn't wish it on anybody.

There are parents of PKU children and adults with PKU who I have contact with through social media, who have started the quest to get Kuvan and other medications the rest of the world seem to have their hands on. We finally get a decision and these adults cannot have access to the medication? And the parents who started the fight for Kuvan 16 years ago.. their children are now too old to receive it?
It is disgusting.
We are all in the same position and EVERY PKU patient, no matter their age, has a RIGHT to the medication they NEED and quite rightly DESERVE.

Q3. The brain does not stop developing until a human is in their 80s. Neurones are developed until that age.

Q4. *[no response given to this question]*

Q5. Being a parent of two young children with PKU, I worry every single day that they will one day refuse or want to come off of diet. I worry for their brains and their bodies and their quality of life.
My children never asked for PKU, and the fact there is Kuvan that is available for them is amazing. But you cannot expect to then take that from them at the age of 18 knowing the damage it can cause.

Q6. *[no response given to this question]*

Q7. *[no response given to this question]*

Q8. *[no response given to this question]*

Q9. *[no response given to this question]*

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. *[no response given to this question]*

Respondent 125

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Current management guidance of PKU recommends 'diet for life' and Kuvan responders will benefit from a reduced reliance on synthetic foods which are often unplalatable. Reverting to a more strict diet in late adolescence, a developmentally difficult period as is well documented, is significantly likely to result in poor adherence and worse outcomes for young adults. Whilst NICE has looked at the evidence FOR remaining on Kuvan it has failed to examine evidence on the potential, negative outcomes associated with NOT continuing on Kuvan treatment. A review of the evidence base for stopping or withholding disease management techniques in similar populations needs to be considered. Given the documented risk of mental health difficulties in those living off diet it is postulated that witholding or stopping treatment in early adulthood/late adolescence could have disastrous effects on individuals mental and physical health and this has not been adequately considered by NICE. As an expert in mental health and the mother of a young child with PKU I would recommend this draft guidance undertakes a comprehensive review in relation to the detrimental impact of stopping treatment at age 18 from a mental and physical health perspective.

Q3. I do not agree with NICE's view

Q4. There is evidence of poor mental health outcomes and poor executive functioning on neuropsychological assessment and on neuro imaging in adults with poor dietary management- this evidence base needs to be considered by NICE.

Q5. Yes - whilst we as a family have coped well my son is on higher levels of protein than many others and therefore could be considered an example of how less restriction has a positive impact on the overall quality of life for children with PKU and their families thus compounding the argument for KUVAN to be made available via the NHS.

Q6. This is not considered relevant for our family but I am aware of many other families who do have this daily struggle. It is a heterogeneous disease which has not been fully accounted for in the guidance.

Q7. Attentional deficits are something my son struggles with and I do worry about his long term attainment at school - any additional treatments that can help such as KUVAN will have lng term benefits in relation to attainment and future successes in life.

Q8. N/A

Q9. As before the heterogeneity of this disease and its management have not been fully considered in this draft proposal and anecdotally I have seen evidence of those from a lower socio economic background struggling much more significantly. I am also aware of my privilege as white, middle class female and therefore feel that inequality across many areas has been gravely overlooked in this guidance.

Q10. *[no response given to this question]*

Q11. *[no response given to this question]*

Q12. *[no response given to this question]*

Q13. A comprehensive review is required and inviting experts from other rare disease groups and service users to review the evidence base for withholding or stopping treatment in early adulthood is urgently required.

Respondent 126

Q1. I do not agree with stopping access to Kuvan at age 18.

Q2. Our daughter is 11 and on 6 exchanges (6 g of proteins/day). Kuvan may change her life, as her diet is so restricted. I can't imagine her having to go back to this very restrictive diet, and this will happen not long before she leaves her family home (she is planning on going to University).

Moreover, it is demonstrated that people develop a taste based on their diet. If she moves on to non-PKU food, there is a high possibility that she won't like the food she is currently eating (if you have never tried them, low-protein bread, pasta, etc., have a very different taste from the not-low-protein products).

Also, she would need to abandon completely food allowed by a higher tolerance on Kuvan.
It seems cruel allowing people to have choices and possibilities, but only to the age of 18. Already a challenging time for many other reasons.

Q3. I do not agree with NICE's view;NICE's statements are contradictory;1. Many studies show that the brain does not stop developing and NICE itself confirms so in the same document. 2. To limit the effects on adults to brain damage is irresponsible, as a great number of studies shows that PKU is/can be the cause of many neurological and mental health issues (e.g., Behavioral, emotional and social problems and adults, lack of focus, seizures, inability to concentrate, etc.)

Q4. A great-uncle that was not on a diet as an adult was unable to keep a job and build a stable life for himself.

Q5. Supporting a child with PKU is an everyday challenge, the changes in a teenager make this even more difficult. Having a teenager getting off Kuvan at such a critical time in their life adds serious difficulties and emotional distress to try and teach the importance of such a difficult diet. Even more when they are supposed to get ready for a life on their own. We would reconsider her move as worried that she would not be able to follow through with the diet and give up the habits that she grew accustomed to during her life on Kuvan.

Q6. We, as carers, spend a great amount of time preparing food, following medical needs (e.g., blood test, prescriptions, etc.), ensuring that the protein supplements are taken as needed, calories intake is adequate every single day, ensuring that the mental health of a person with PKU is not affected by the limitations of their condition (which can cause social rejection and can lead to refusal of the diet). I had to give up work opportunities because they would not allow me the time to support my daughter as needed.

Q7. We agree - When poor, our daughter's levels increase, bringing headaches and agitation. The same happens during growth spurts or intense physical activity, if her calories intake falls under a certain level, causing catabolism and consequent release of phenylalanine that ends up in her neurological system.

Q8. Mental health issues are not addressed for PKU as we as parents try to support them and look within the community for help, as hospitals and medical staff is often too overworked or unable to offer this kind of support

Q9. *[no response given to this question]*

Q10. This is very serious, as, even not considering the unfair and avoidable damage to the family. a newborn with health issue is a much higher cost for the society.

Q11. The challenges of the diet are extreme, especially when the tolerance is low - pregnancies are emotionally and physically a major change that is to be supported by the society for the wellbeing of the mother as well as of the newborn. An infinite number of studies show how the dietary habits of the mother affect the fetus - PKU is one additional serious component that needs to be addressed

Q12. Costs for Kuvan pale when compared, as highlighted above, to the financial, social, emotional costs of an unhealthy newborn

Q13. Low-protein food is expensive. Kuvan would offset some of these costs while also significantly improving people's lives and avoiding ulterior costs due to other health issues (such as the ones mentioned before - mental health, diabetes, etc.)

Organisation name – Stakeholder or respondent

British Dietetic Association

National Society for Phenylketonuria

Disclosures

- **Direct – financial**- Birmingham Children's Hospital have received research funds from Nutricia, Vitaflo, Biomarin, APR, Metax, Galen, Mevalia
- Received Consultancy fees (given to Birmingham Children's Hospital PKU research fund) from Meta Healthcare, Arlo, Nutricia, Apr, Galen and Biomarin.

Name of commentator person completing form:

Anita MacDonald

[redacted]

Comment number:

1. WHY SAPROPTERIN SHOULD NOT BE STOPPED AT THE AGE OF 18 YEARS

The draft proposal to stop sapropterin at the age of 18 years is not in the best interests of patients with PKU and I cannot support this. This proposal contradicts the recommendations of the PKU European Guidelines 2017, the USA PKU guidelines and the PKU MRC 1993 group guidelines that treatment should be for life in PKU. By giving this recommendation, NICE is giving an overwhelming message that treatment does not matter in adulthood.

It is irrational to relax protein intake in childhood, only to restrict it later in adulthood. It is expected that the proposed recommendation of NICE will lower patient motivation at the age of 18 years; it could also lead to patients failing to attend their metabolic clinics as they consider they are not being offered a realistic or workable treatment option.

The dietary treatment for PKU is particularly arduous, unpalatable and consists of a limited range of foods. Many of the foods that are permitted are high in sugar and are discouraged for the general population as they are unhealthy. We currently have no option but to advise these foods as part of a low phenylalanine diet in PKU. See Table 1 for the list of low

protein/exchange free foods that are allowed without measurement. Although the dietary difficulties have already been described to NICE, it is necessary to re-explain the gruelling nature of the dietary treatment and the daily struggles faced by patients. It is harsh and unrealistic to expect any individual with PKU to resume such a difficult, unappetizing and complex diet when research and experience repeatedly shows that many patients are unable to restart dietary treatment once it has stopped or been substantially relaxed (*see section 'why a dietary treatment only option is inadequate for adults with PKU'*). There is overwhelming evidence to demonstrate that most patients are unable to sustain long term dietary treatment (Table 2) and that blood phenylalanine levels increase with age (Medford et al 2017). It is highly likely that stopping sapropterin at the age of 18 years will lead to cessation of treatment.

Many young children with PKU develop rigid eating patterns. They are food neophobic and are frightened to try new foods; this is commonly seen from early childhood (Evans et al 2015, MacDonald et al 1997). I have experience of caring for at least 15 children on sapropterin (either on clinical trials or funded by IFR's). We work with children to gradually expand their diet to include a wider range of nutritious foods; this may take many months or even years to accomplish but it is worthwhile when children develop a healthier eating pattern. Thereby, at the age of 18 years, it is unthinkable that patients are expected to return to an abnormal eating patterns they followed in early childhood prior to sapropterin therapy. They will have acquired a taste for higher protein foods. Some of the children in our clinic have been on sapropterin for 9 years; many eat higher protein foods including meat or fish daily. They will also eat regular bread and pasta. They do not use low protein special foods. They take minimal protein substitute. Therefore, they are unlikely to tolerate a low phenylalanine diet again at a later age.

It also appears that the age of 18 years is an arbitrary cut off point. Eighteen years is a difficult developmental age when physical growth stops but brain function continues to develop. The brain is still maturing, and strengths and vulnerabilities continue to emerge. It is a time of life when little is normative. It is a period of frequent change that covers many aspects of life: including hospital transition, leaving school, living independently, going to work or University. It is a time when individuals face significant challenges and are expected to assume new responsibilities and obligations.

Generally, the process of becoming an adult is more gradual and varied today than in the past. Young people take longer to achieve economic and psychological autonomy and early adulthood experiences vary greatly by gender, race and ethnicity, and social class. Many may struggle to find a path to employment, economic security, and well-being. It is important that young adults with PKU try to maintain optimal metabolic control to help them fully utilise any opportunities they are given throughout this process. Adults with PKU who have showed much academic potential as teenagers describe dropping out of University because they have been unable to adhere to their only treatment option of dietary management with consequential result of loss of metabolic control which then impacts on executive function and mental health.

Early adulthood is generally a time of heightened psychological vulnerability and onset of serious mental health disorders, with higher rates of psychological distress; problems compounded by failure to recognize illness or to seek treatment. Suddenly exposing patients

with PKU to higher phenylalanine levels at the age of 18 years, may increase the risk of mental health issues. It may lead to mood instability, impulsivity, recklessness, and anger. Young adults may participate in risk taking behaviour and young women with PKU may be more vulnerable to maternal PKU syndrome due to unprotected sexual activity. In addition, marginalized young adults, such as those leaving foster care, those with low IQ and autism, and children of low-income immigrant families, are less likely to experience a successful transition to adulthood, and will be particularly vulnerable if sapropterin is stopped.

Thereby, the age of 18 years is a critical window of development. It is important that PKU care is not mismanaged at this age. Success or failure in navigating life's paths can set young adults on a course that will strongly affect the future outcome of their adult lives. Allowing patients to continue sapropterin will improve their lives; it will enable them to be independent and enter into the workforce with continued productivity. Stopping sapropterin when people with PKU are in full time education is not appropriate. This is setting people up to fail university education and will cause long term harm and potential financial instability. The decision to offer dietary treatment only from the age of 18 years will magnify inequality, with lasting effects throughout adulthood, with potential impact on morbidity inequalities in later adulthood.

Furthermore, by stopping sapropterin, patients will require intensive dietary education at the age of 18 years. They will need considerable re-education with a new clinical team of adult specialists that has not had time to establish trust and rapport with their patients. This will have financial implications that has not been calculated in the cost model.

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Table 1. The range of foods that can be eaten without measurement/restriction by someone with PKU. This illustrates the limited the range of food that an 18 year old person with PKU would be expected to eat without measurement after years of following a relaxed protein intake. This indicates the monotony of the diet and the level of self-control that adult patients must demonstrate.

Food Groups	Examples of suitable foods that can be eaten without measurement
Fruits and vegetables	Fruits and vegetables that can be given without measurement are fruits and vegetables containing ≤75 mg/100g of phenylalanine.
Fats	Butter, margarine, ghee, lard, dripping and vegetable oils.
Starches:	Cassava flour, arrowroot, cornflour, custard powder, potato starch, sago, tapioca, and tapioca starch.
Sugars	Sugar, glucose, jam, honey, marmalade, golden syrup, maple syrup, fruit sorbets, ice lollies, sweets containing ≤0.5g protein/100g
Miscellaneous:	Vegetarian jelly, agar-agar, salt, pepper, herbs, spices and vinegar; food essences and colouring; fruit/vegetable 'tabletop' sauces and 'cook in sauces' containing ≤1.0g protein/100g.
Drinks	Water, squash, lemonade, cola drinks and fruit juice, black tea, fruit tea, green tea, coffee, tonic water, soda water and mineral water, providing all are aspartame free (this requires careful reading of ingredient labels). Other plant drinks e.g., oat milk that contain some phenylalanine should be calculated in the diet.
Low protein special foods	A selection of low protein breads, flour mixes, pizza bases, pasta, biscuits, egg replacers, and milk-replacements are available.

Other evidence

2. WHY A DIETARY TREATMENT ONLY OPTION IS INADEQUATE FOR ADULTS WITH PKU AND WHY THEY SHOULD HAVE EQUAL ACCESS TO ALTERNATVE TREATMENT OPTIONS

By stopping sapropterin in early adulthood, in the 20 to 30% of patients who are BH4 responsive, NICE are leaving this group of patients without a sustainable treatment option in adult life.

- It is well established that many adult patients are unable to adhere to long term dietary management. Adherence with the PKU diet becomes increasingly challenging as

patients' age, especially as patients transition from adolescence to adulthood. There is plenty of data to show that a high proportion of adult patients are unable to maintain blood phenylalanine levels within target range on dietary management only (not just the 20-30% that NICE suggest in their report). (see Table 2 for evidence). Metabolic control in PKU worsens with age. Equally evidence from other chronic conditions (diabetes, hypertension) shows low patient adherence rates with special diets only but a combination of treatment strategies is a more successful policy. It is also widely accepted that in many other disorders that adherence to special diets is one of the most difficult aspects of treatment, particularly when diet therapy is initiated in adulthood.

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Table 2. A summary of blood phenylalanine control from worldwide studies

Study	Country	Participants	Blood Phe target range	Results
Walter et al 2002	**UK and Australia**	Results from 4 centers were audited between 1994–2000. Data were available from 330 patients. Their median age at the start of the study was 4 y (range 0–19).	**<5 y:** 360 µmol/l **5-10 y:** 480 µmol/l **≥10 y:** 700 µmol/l	The median proportion of samples with Phe concentrations above those recommended was less than 30% for those younger than age. 10 y but almost 80% for those aged ≥15 y. The median frequency of blood sampling, expressed as a proportion of that recommended, was > 80% for patients < 10y but < 50% at 15y.
Meli and Bianca 2002	**Catania, Italy**	95 PKU patients: 4 (< 1 y), 13 (aged 1-6 y), 26 (aged 6-10 y), 17 aged (10-14 y) and 35 (>14 y).	**-**	Phe levels were greater than the recommended value in none of the patients < 1 y, in 8% of the 1-6 y, in 18% of the 6-10 y, in 40% of the 10-14 y, and in 70% >14 y.
Mundy et al 2002	**London, UK**	All patients with PKU seen from 2001-2002.	**≥10 y:** 700 µmol/l	Proportion with Phe greater than recommended 74.3% (28.9–100). Mean blood Phe (µmol/l): 780.6 (653-948).

		96 of 180 patients were following a Phe-restricted diet with a mean age of 26 y (15-52 y).		
Walter and White 2004	**Manchester, UK**	Data from 75 patients (of whom 42 were male) were available for analysis.	**>10 y:** 700 µmol/l	At 10 y of age <20% of samples were above the recommended level, but this had increased to 75% by 19 y. Similarly, the frequency of blood sampling fell from a mean of 83% of that recommended to under 51% by 20 y.
Ahring et al 2011	**Europe**	A survey was conducted to compare blood Phe control achieved in diet-treated patients with PKU of different age groups in 10 European centers. Overall, 1921 patients on dietary treatment met the inclusion criteria; 115 patients in 3 centers received LNAA and 17 patients also received BH4.	**Different target levels in each centre.**	**Age:** Median Phe (µmol/l) / *Median % blood samples with Phe within or below target* / Median % blood samples returned according to guidelines **<1 y:** 175 (137–195) / *88 (82–96)* / 102 (100–112) **1-3 y:** 230 (206–246) / *74 (67–86)* / 100 (92–121) **4-10 y:** 287 (254–327) / *74 (58–85)* / 92 (90–117) **11-16 y:** 465 (347–527) / *89 (64–95)* / 83 (66–87) **Adults:** (416) 777 (604–855) / *65 (44–88)* / 55 (51–75)
Das et al 2014	**Hannover, Germany**	72 adults contacted. Only 51 entered the study due to loss of follow up.	**0-10 y:** < 240 µmol/l **10-15 y:** < 900 µmol/l **> 15 y:** 1200 µmol/l	**Current levels (mean concentration)** **PKU diet:** ≈700 µmol/l **Vegan diet + protein substitute:** ≈950 µmol/l **Vegan:** ≈900 µmol/l **Normal food:** ≈1110 µmol/l **Lifetime Phe levels (mean concentration in µmol/l)** **PKU diet:** ≈300 (0-10 y), ≈550 (10-15 y), ≈700 (>15 y). **Vegan + protein substitute:** ≈500 (0-10 y), ≈450 (10-15 y), ≈800 (>15 y). **Vegan:** ≈200 (0-10 y), ≈700 (10-15 y), ≈850 (>15 y). **Normal food:** ≈380 (0-10 y), ≈850 (10-15 y), ≈1050 (>15 y).
Gramer et al 2016	**Heidelberg, Germany**	36 PKU patients (15 males and, 21 females) with mean		Mean Phe level was 677 µmol/l (SD 506; 42-1943). For patient subgroups 'children', 'adolescents' and 'adults'

		age 17.2 y (SD 10.1; range 5.1-38.5). All patients diagnosed by NBS and early and continuously treated.		mean Phe was 242 µmol/l (SD 138; 97-557), 980 µmol/l (SD 414; 393-1719) and 919 µmol/l (SD 523; 42-1943), respectively.
Mütze et al 2016	**Leipzig, Germany**	All PKU patients transferred from pediatric to adult care between 2005 and 2015 were identified. 96 PKU patients (56 females and 40 males) with a median age of 32 y (18-62) were included. Late diagnosed and early treated patients included.	**-**	In previous 3 y period, 81% (44 females and 32 males) of the transferred patients kept contact to the adult outpatient clinic. **Median** (range) **of individual mean Phe of all transferred PKU patients did not differ over the 10-year period**: 673.0 (213.0-1381.1) µmol/l **Median (range) Phe during 6th year of life (n=74 patients):** 307.3 (92.1-1246.6) µmol/l **Median (range) Phe during 18th year of life (n= 71 patients):** 587.4 (52.5-1454.6) µmol/l **Current median (range) of last 3 Phe levels (n=96):** 658.7 (109.1-1458.5) µmol/l
Jurecki et al et al 2017	**USA**	Data collected July to September 2015 44 clinics from USA. The median number of actively managed patients per clinic was 78 (range 15-275 patients; note that only clinics with ≥15 patients entered study). In total, 3772 actively managed PKU patients, 41% of which were adults.	**Different targets across different centers.**	The proportion of total patients considered lost to follow up increased with age, from 10% for the 0-4 y to 55% in the 30+ age group. Overall, an estimated 32% of all PKU patients in respondent's clinics were lost to follow-up. **<u>% patients within target (120-360 µmol/l):</u>** **0-4 y:** 78% **5-12 y:** 67% **<u>% patients within target (120-600 µmol/l):</u>** **13-17 y:** 74% **18-29 y:** 59% **>30 y:** 45%
Mlčoch et al 2018	**Prague, Czech Republic**	Total patient number =174, mean age 14 y (11; 5–22).	**-**	**N= 167** **Mean Phe concentration, µmol/L (median; IQR)** **0-3 y:** 214 (182; 109-254)

				4-6 y: 215 (218; 103-315) **7-10 y:** 297 (242; 170-335) **11-14 y:** 364 (345; 206-482) **15-18 y:** 556 (618; 363-726) **>18 y:** 771 (787; 539–938)
Cazzorla 2018	**Italy**	111 PKU (61F/50M) across 5 centres, mean age 24y (19-30y)	**120 to 600** umol/L	22%<600 umol/L 48% >600 umol/L 19%>1000 umol/L

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Walter JH, White FJ. Blood phenylalanine control in adolescents with phenylketonuria. Int J Adolesc Med Health. 2004 Jan-Mar;16(1):41-5.

Ahring K, Belanger-Quintana A, Dokoupil K, et al. Blood phenylalanine control in phenylketonuria: a survey of 10 European centres. Eur J Clin Nutr. 2011 Feb;65(2):275-8.

Das AM, Goedecke K, Meyer U, et al. Dietary habits and metabolic control in adolescents and young adults with phenylketonuria: self-imposed protein restriction may be harmful. JIMD Rep. 2014;13:149-58.

Gramer G, Haege G, Langhans CD, et al. Long-chain polyunsaturated fatty acid status in children, adolescents and adults with phenylketonuria. Prostaglandins Leukot Essent Fatty Acids. 2016 Jun;109:52-7.

Mutze U, Thiele AG, Baerwald C, et al. Ten years of specialized adult care for phenylketonuria - a single-centre experience. Orphanet J Rare Dis. 2016 Mar 24;11:27.

Garcia MI, Araya G, Coo S, et al. Treatment adherence during childhood in individuals with phenylketonuria: Early signs of treatment discontinuation. Mol Genet Metab Rep. 2017 Jun;11:54-58.

Jurecki ER, Cederbaum S, Kopesky J, et al. Adherence to clinic recommendations among patients with phenylketonuria in the United States. Mol Genet Metab. 2017 Mar;120(3):190-197.

Mlcoch T, Puda R, Jesina P, et al. Dietary patterns, cost and compliance with low-protein diet of phenylketonuria and other inherited metabolic diseases. Eur J Clin Nutr. 2018 Jan;72(1):87-92.

Cazzorla C, Bensi G, Biasucci G, Leuzzi V, Manti F, Musumeci A, Papadia F, Stoppioni V, Tummolo A, Vendemiale M, Polo G, Burlina A. Living with phenylketonuria in adulthood: The PKU ATTITUDE study. Mol Genet Metab Rep. 2018 Jul 11;16:39-45.

Ford et al in 2018 from a survey that reported the experiences of over 300 adults with PKU, said that many described their dietary management as complex and impractical and so abandoned treatment, with some withdrawing from medical care [Ford et al 2018]. Some said that the thought of diet recommencement was almost inconceivable. Some adults who remained on diet but maintained higher blood phenylalanine levels than target ranges had lifelong feelings of self-failure. Adults who received support from partners or family coped better with dietary treatment.

Reinstitution of diet after relaxation has long been recognised to be problematic (Schuett et al 1985). Many adults have difficultly re-establishing dietary control after a period off diet. In a Polish study, only 29/53 adults managed to return to a low phenylalanine diet for 3 months, and 10 completed a 9-month study protocol [Bik-Multanowski et al 2008]. Patients generally do better only if they have a good support network, perceive that their symptoms improve with treatment, and experience that their dietary treatment is manageable [Finkelson et al 2001]. Many adults try repeatedly to recommence dietary treatment but struggle to sustain it beyond a few weeks. Once they are on diet, if they transiently falter from their strict routine, patients lose motivation and capacity to cope with the demands of dietary treatment and are unable to continue. Patients have a constant sense of failure. The following are some of the unreported survey quotes about returning to dietary treatment from the *Living with PKU survey* conducted by the NSPKU in 2018.

'My diet was relaxed at 13yrs and then stopped. I came off diet until preconception diet at 30yrs. I enjoy food and eating socially, it's very hard to restrict protein once you've eaten a normal diet for so many years. I have tried to return to diet numerous times, I struggle with the planning and organisation and the time it takes, and also the restriction. I wish I had never been allowed to come off diet. I am off diet'.

'To be good at the diet you need full support from home and medical. If one part is missing, you fall off the wagon. Then due to the effects of high Phe levels (bad concentration, lethargy, low self-confidence and anxiety) it is IMPOSSIBLE to claw yourself back. It's a cycle of failure and depression'.

'I have difficulty planning tasks, partly due to my PKU, and find it difficult to plan a diet or remember to take formula. I find normal life hard and overwhelming in itself without strict diet and formulas to think about, due to my severe anxiety and depression'.

‘Difficult with a husband working long hours and 4 children, tired, bored, socially difficult. Lack enthusiasm for the food choices and suffer with hunger pangs’.

Overall, non-adherent patients report more emotional issues related to PKU [Borghi et al 2020]. Patients receiving BH4 report lower practical and emotional impacts because of lower burden of care associated with the diet [Bosch et al 2015].

Ford S, O'Driscoll M, MacDonald A. Living with Phenylketonuria: Lessons from the PKU community. Mol Genet Metab Rep. 2018 Oct 18;17:57-63.

Schuett VE, Brown ES, Michals K. Reinstitution of diet therapy in PKU patients from twenty-two US clinics. Am J Public Health. 1985 Jan;75(1):39-42.

Bik-Multanowski M, Didycz B, Mozrzymas R et al. Quality of life in noncompliant adults with phenylketonuria after resumption of the diet. J Inherit Metab Dis 2008;31 Suppl 2:S415-8.

Finkelson L, Bailey I, Waisbren SE. PKU adults and their return to diet: predicting diet continuation and maintenance. J Inherit Metab Dis. 2001 Aug;24(4):515-6.

Borghi L, Moreschi C, Toscano A, Comber P, Vegni E. The PKU & ME study: A qualitative exploration, through co-creative sessions, of attitudes and experience of the disease among adults with phenylketonuria in Italy. Mol Genet Metab Rep 2020;23:100585.

Bosch AM, Burlina A, Cunningham A et al. Assessment of the impact of phenylketonuria and its treatment on quality of life of patients and parents from seven European countries. Orphanet J Rare Dis 2015;10:80.

There are many barriers to long term dietary adherence in PKU and it is it is associated with a high burden of care. These issues have been well described in the literature and are described in Table 3. Treatment burden increases with co-morbidities such as cognitive and mental health issues. In childhood, these burdens are carried by parents/carers. But some adult patients are overwhelmed with the complexity of self-managing their special diet and are unable to effectively sustain this long term, which then negatively affects their wellbeing and outcome. Treatment burden is not assessed within metabolic clinics, but it is important in determining patient capacity to adhere to this treatment regimen.

In addition, some adult patients with PKU have low nutrition literacy which further disadvantages their ability to adhere to a low phenylalanine diet. Nutrition literacy is defined as “the degree to which individuals have the capacity to obtain, process, and understand nutrition information and skills needed in order to make appropriate nutrition decisions” [Silk et al 2008] and is a known predictor of dietary adherence [Taylor et al 2018]. Nutrition literacy predicts adherence to healthy/unhealthy diet patterns in adults with a nutrition-related chronic condition. **In adults with PKU, limited health literacy is common and disproportionately affects minority populations, older adults with PKU, patients with lower educational attainment and lower incomes.**

Silk KJ, Sherry J, Winn B et al. (2008) Increasing nutrition literacy: testing the effectiveness of print, web site, and game modalities. J Nutr Educ Behav 40, 3–10)

Taylor MK, Sullivan DK, Ellerbeck EF, Gajewski BJ, Gibbs HD. Nutrition literacy predicts adherence to healthy/unhealthy diet patterns in adults with a nutrition-related chronic condition. Public Health Nutr. 2019 Aug;22(12):2157-2169

Table 3. Barriers to long term adherence with a low phenylalanine diet in adults with PKU

Patient barrier	Impact
Financial constraints/ prescriptions costs/ costs of low protein specialist foods/loss of earnings due to part-time work/low income	Alters and limits access to low protein foods and suitable fruits and vegetables; reduces ability to maintain low phenylalanine diet.
Burdensome treatment	Onerous workload that requires considerable patient management time. Treatment burden increases the risk of non-adherence. In PKU, dietary management involves avoiding 80% of normal dietary protein. Patients must think continuously about diet, maintain strict dietary routines, and meticulously plan every activity that involves food. Extra time shopping, carefully evaluating food labels to source suitable low protein foods, taking of protein substitute at least three times daily, planning daily phenylalanine consumption, preparing low phenylalanine meals (involving extra cooking), monitoring phenylalanine intake, blood phenylalanine monitoring and attending metabolic clinics. Adults with PKU find sustaining dietary treatment along side worklife or university very difficult. Patients who work shift patterns or nights have particular difficulty with sustaining dietary routines. Adults with PKU who have their own children have to prioritise their children's dietary needs before their own.
Lack of food choice	Only a limited number of suitable low protein foods can be eaten without restriction. Many foods are commonly high in sugar, starch and fat and considered unhealthy for the general population. **See table 1.**
Previously followed a normal diet	Once patients have developed a taste for high protein foods it is difficult to successfully return to a low protein diet. People will have difficulty in readjusting eating habits that have been formulated over many years.
Health literacy	Poor knowledge of diet, limited cooking skills, low knowledge of food suitability, limited meal choice; inability to read and interpret protein amounts on food labels, unable to estimate protein exchanges, difficulty accessing supplies of protein substitutes/low protein foods.

Poor taste/acceptability of protein substitutes	Unpleasant memories of the protein substitute taste, smell and texture from childhood, lead to its low acceptability, and gastointestinal symptoms such as reflux and constipation. Some patients find this aspect of dietary treatment intolerable. Once it has been stopped, it is very difficult to start taking this again. Partial adherence to protein substitutes will lead to poor metabolic control and risks of nutritional deficiency.
Poor acceptance of diet	Poor taste and refusal of low protein foods leading to hunger.
Impact of PKU on IQ, executive function and mood	Low IQ (associated with poor childhood blood phenylalanine control) and poor executive functioning affects the ability to self-manage a low protein diet due to the daily organisation and planning required. Low mood may hinder the ability of people to comply by reducing self-control and motivation. Insecurities lead to constant feeling of failure due to inability to sustain dietary management.
Food insecurity	Some people live with fear about accessing sufficient food supplies. This is caused by difficulty in accessing suitable low protein foods in supermarkets and GP refusal to prescribe protein substitutes and low protein foods.
Loss of social support	In adulthood, the loss of social support from family who understood the treatment well is difficult. For some adults, it will limit their capacity to adhere to dietary restrictions.
Health care services	Long travel times to metabolic clinics, lack of transportation, and stress associated with appointments. Lack of empathy/understanding by some health care professionals. In clinics, clinicians spend limited time supporting and educating, but time on reviewing blood phenylalanine test results emphasising the need for dietary adherence. Low protein food and protein substitute prescription refusals by GPs.
Low socialisation and social stigma	Inability to find suitable foods when eating out or in social gatherings. Eating different food from others in public causes unwanted attention.
Poor relationship with food	Many report guilt feelings about poor dietary adherence and have less food enjoyment (Ford et al 2018). Some have disordered eating.
Emotional burden	Many patients with PKU have been exposed to biased and persistant discriminatory behaviour about their dietary treatment which causes emotional distress and is a disincentive to maintain dietary treatment.

3. EVIDENCE FOR THE NEED FOR LIFELONG CARE IN PKU AND CHRONIC ISSUES EXERIENCED BY ADULTS WITH PKU

The main goal of management in PKU is the long-term protection of neurocognitive and psychological functions. For years after the start of newborn screening (in the 1960's), there was controversy over the length of time treatment was necessary. Today, however, there is an abundance of data showing that blood phenylalanine levels maintained within target range are crucial for healthy brain and neuropsychological functioning throughout life.

Adults with PKU experience many chronic issues (depression, anxiety, low mood, poor executive function), indicating the ongoing negative effects of high blood phenylalanine levels on the brain and psychological functioning in adulthood. There is almost universal consensus among clinicians that "treatment for life" is the best approach for the early-treated population. Although NICE suggest that dietary treatment is given as the only treatment option, it is clear from the evidence presented that many adults cannot adhere to this.

Associated with the absence of practical treatment options is the high rate of patients who are 'lost to follow up' who should attend an adult metabolic clinic. Unfortunately, there is no knowledge about their clinical outcome. It is suggested that around 50% of adult patients with PKU in the UK have been lost to follow up [Burton et al 2005]. A European survey on management of adult patients reported that the majority of patients with PKU in active follow up were aged under 30 years, suggesting that there is a 'lost generation' of older adult patients [Trefz et al 2015].

Even those adult patients who remain in follow up do not have their neurocognitive performance closely monitored and there is no patient registry scrutinising adult clinical outcome in the UK. Trefz et al [Trefz et al 2015] reported that across Europe, only 26 % of health care professionals routinely perform neurocognitive testing in adult patients. Thereby medics, psychiatrists, and psychologists are unlikely to be aware of the full extent of neuropsychiatric comorbidities associated with this disorder.

Burton H, Sanderson S. Metabolic Pathways: Networks of Care. A needs assessment and review of services for people with inherited metabolic disease in the United Kingdom. Cambridge: Public Health Genetics Unit. 2005

Trefz FK, van Spronsen FJ, MacDonald A, Feillet F, Muntau AC, Belanger-Quintana A, Burlina A, Demirkol M, Giovannini M, Gasteyger C. Management of adult patients with phenylketonuria: survey results from 24 countries. Eur J Pediatr. 2015 Jan;174(1):119-27.

WHAT IS KNOWN ABOUT CLINICAL OUTCOME IN ADULT PATIENTS?

- Evidence from a systematic review demonstrates that significant sub-optimal outcomes exist in early treated adults with PKU. High blood phenylalanine levels lead to both acute and chronic neuropsychiatric symptoms. NICE suggest that these

symptoms are reversible with dietary treatment, but the evidence clearly shows that the majority of patients with PKU cannot sustain dietary treatment and maintain blood phenylalanine levels below 600 µmol/L, so dietary treatment alone is not adequate to reverse and prevent recurrence of symptoms long term. Patients who have better outcome generally have achieved blood phenylalanine control within treatment guidelines throughout their life.

- Impairment in psychiatric, behavioural, and neurocognitive function often reflect the timing, duration, and intensity of phenylalanine exposure. There is wide variability/heterogeneity between individuals. It is unknown if dietary treatment alone can lead to a full remission in psychiatric illness.

- Some adults have low IQ due to poor phenylalanine control in childhood – therefore neurological damage is permanent. There is much evidence to suggest that the inability to sustain good metabolic control in childhood is associated with a decline in IQ score and executive function and will have a negative influence in adulthood (Jahja et al. 2017; Koch et al. 2002; Waisbren et al. 1980). For example, Jaha et al 2017 showed that high blood phenylalanine levels in childhood, affect adult cognitive flexibility, executive motor control, executive function in daily life and adult mental health. Weglage (2013) also showed that high blood phenylalanine levels in childhood and adolescence were related to poorer IQ, information processing and attention in adulthood. Lower IQ lessens the patient ability to manage a low phenylalanine diet. Low IQ is linked with social disadvantage (low paid job, living in poverty), which in turn lessens the ability to apply the stringent dietary treatment.

Jahja R, Huijbregts SCJ, de Sonneville LMJ, van der Meere JJ, Legemaat AM, Bosch AM, Hollak CEM, Rubio-Gozalbo ME, Brouwers MCGJ, Hofstede FC, de Vries MC, Janssen MCH, van der Ploeg AT, Langendonk JG, van Spronsen FJ. Cognitive profile and mental health in adult phenylketonuria: A PKU-COBESO study. Neuropsychology. 2017 May;31(4):437-447.

Koch R, Burton B, Hoganson G, Peterson R, Rhead W, Rouse B, Scott R, Wolff J, Stern AM, Guttler F, Nelson M, de la Cruz F, Coldwell J, Erbe R, Geraghty MT, Shear C, Thomas J, Azen C. Phenylketonuria in adulthood: a collaborative study. J Inherit Metab Dis. 2002 Sep;25(5):333-46.

Waisbren SE, Schnell RR, Levy HL. Diet termination in children with phenylketonuria: a review of psychological assessments used to determine outcome. J Inherit Metab Dis. 1980;3(4):149-53.

Weglage, J., Fromm, J., van Teeffelen-Heithoff, A., Möller, H. E., Koletzko, B., Marquardt, T., et al. (2013). Neurocognitive functioning in adults with phenylketonuria: Results of a long term study. Molecular Genetics and Metabolism, 110(Suppl.), S44-S48.

- Feldmen et al 2019 showed that older adult patients (> 42 years) with PKU showed poorer information processing and attention compared to young adult patients (< 42 years) and controls. IQ was significantly correlated to blood phenylalanine levels in

patients´ childhood and adolescence, and phenylalanine levels had been higher in the adolescent years of older adult patients.

Feldmann R, Osterloh J, Onon S, Fromm J, Rutsch F, Weglage J. Neurocognitive functioning in adults with phenylketonuria: Report of a 10-year follow-up. Mol Genet Metab. 2019 Mar;126(3):246-249.

- Many studies have shown PKU patients had significantly worse test results in memory, problem-solving skills, and strategy (Christ et al. 2010, Jahja et al. 2017, Bartus 2018). There is no evidence to show that this improves with time.

Christ SE, Huijbregts SC, de Sonneville LM, White DA. Executive function in early-treated phenylketonuria: profile and underlying mechanisms. Mol Genet Metab. 2010;99 Suppl 1:S22-32.

Jahja R, Huijbregts SCJ, de Sonneville LMJ, van der Meere JJ, Legemaat AM, Bosch AM, Hollak CEM, Rubio-Gozalbo ME, Brouwers MCGJ, Hofstede FC, de Vries MC, Janssen MCH, van der Ploeg AT, Langendonk JG, van Spronsen FJ. Cognitive profile and mental health in adult phenylketonuria: A PKU-COBESO study. Neuropsychology. 2017 May;31(4):437-447.

Bartus A, Palasti F, Juhasz E, Kiss E, Simonova E, Sumanszki C, Reismann P. The influence of blood phenylalanine levels on neurocognitive function in adult PKU patients. Metab Brain Dis. 2018 Oct;33(5):1609-1615.

- There are a small but increasing number of case reports in recent years that provide evidence that some adult PKU patients develop severe neurological symptoms in later adulthood (**see the first part of Table 4- for information about case studies in the literature**). Some of these cases are from the UK. They demonstrate that severe decline in neurological function occurs despite relatively normal function for a substantial period. They demonstrate the vulnerability of the brain to high phenylalanine levels. It is possible that there are many similar cases, but they remain unreported by clinics. Not all symptoms have reversed on dietary treatment. Also, authors generally do not report the longer-term outcome of these cases.

Pérez-Dueñas B, Valls-Solé J, Fernández-Alvarez E, et al. Characterization of tremor in phenylketonuric patients. J Neurol. 2005; 252:1328-1334.

Velema M, Boot E, Engelen M, Hollak C. Parkinsonism in phenylketonuria: a consequence of dopamine depletion? JIMD Reports. 2015;20:35-8.

- There is widespread white matter compromise in individuals with PKU, which is exacerbated by increasing age. *Hawks Z, Hood AM, Lerman-Sinkoff DB, Shimony JS, Rutlin J, Lagoni D, Grange DK, White DA. White and gray matter brain development in children and young adults with phenylketonuria. Neuroimage Clin. 2019;23:101916*

- It has been observed that serotonin and to a lesser extent dopamine metabolites are reduced in adult PKU patients and correlate with specific gray matter atrophy patterns.

Pilotto A, Blau N, Leks E, Schulte C, Deuschl C, Zipser C, Piel D, Freisinger P, Gramer G, Kölker S, Haas D, Burgard P, Nawroth P, Georg H, Scheffler K, Berg D, Trefz F. Cerebrospinal fluid biogenic amines depletion and brain atrophy in adult patients with phenylketonuria. J Inherit Metab Dis. 2019 May;42(3):398-406.

- A range of anxiety disorders, including generalized anxiety, panic disorder, specific phobias, and obsessive-compulsive disorder have been reported in PKU and have been associated with low serotonin in the brain in adults with PKU. Rates of depression are considered higher in adults with PKU than the general population. Recent data from the adult PKU clinic in Manchester showed that approximately 75% of the clinic population (n=244) had a 2-year average blood phenylalanine level of >600 µmol/l and this group were more likely to have a diagnosis of low mood, depression, anxiety or mood swings, but only low mood reached statistical significance ($p < 0.05$). They suggested that many adult PKU patients may be lost to follow up, and therefore may be receiving treatment for mental health conditions in the community. Ford et al 2018, reported that in >300 adult patients with PKU from the UK, that 40%, (n=131/331) used antidepressants and 18% (n=60/334) used anxiolytics.

Altman G, Hussain K, Green D, Strauss B, Wilcox D Mental health diagnoses in adults with phenylketonuria: a retrospective systematic audit in a large UK single centre. Submitted for publication to JIMD.

Ford S, O'Driscoll M, MacDonald A. Living with Phenylketonuria: Lessons from the PKU community. Mol Genet Metab Rep. 2018 Oct 18;17:57-63.

- Table 4 demonstrates the recent wealth of studies and care reports that have reported on clinical outcome in adult patients with PKU

Table 4: Studies showing clinical outcome in adult patients with PKU

Author (year)	Country	No. subjects (gender)	Age of subjects (mean/median)	Study type	Type of treatment/ measurements	Age stopped diet	Blood Phe control	Patient outcome /Conclusions
Case reports								
Villasana (1989)	USA	2 PKU (2M)	28y 18y	Case reports	Case A: - diagnosed at 3y. - increased seizure frequency and rapidly progressive spasticity. - leg weakness and stiffness. - marked reduction in biogenic amine neurotransmitter metabolites in cerebrospinal fluid. Case B: - diagnosed on newborn screening. - decreasing school performance. - difficulties with concentration, fine hand tremor, difficulty walking. - cerebrospinal fluid biogenic amine neurotransmitter metabolites significantly reduced.	Case A: strict diet 3-12y Case B: stopped diet ay 6y	Case A: Phe before diet: 1068 µmol/L On diet 2 months: 900 µmol/L On diet 3 months: 216 900 µmol/L Case B: Phe before diet: 1644 µmol/L	- MRI in both cases showed multiple areas of increased signal intensity in cerebral white matter. Case A: - Diet therapy reduced serum Phe levels, improved symptoms of hypertonicity and cerebrospinal fluid neurotransmitter metabolites became normal. - 2 months after initiation of diet, gait improved. Case B: - attempts at re-institution of diet were unsuccessful and he was lost to follow-up.
Thompson (1990)	UK	7 PKU (4 ETPKU) (2F/5M)	Mean age: 23.4y (19-29y)	Case reports	- patients developed neurological disability in adolescence or early adulthood (13-25y): quadriparesis, ataxia, paraparesis, epilepsy, tremor, dystonia.	Mean age stopped diet: 11y (7-18y)	Mean Phe: 1440 umol/L (900-2000)	- 2 patients showed marked clinical improvement when a strict diet was resumed. - MRI from one patient showed abnormalities that appeared after cessation of dietary treatment and resolved after diet was resumed.
Aung (1997)	USA	1 ETPKU (1M)	19y	Case report	- Diagnosed at birth, discontinued diet and follow-up at 14y. Continued to self-restrict meat & dairy. - presented with cold symptoms, tiredness, forgetfulness, inability to concentrate, pale, with a red, smooth tongue.	14y	On presentation: 1270 umol/L	- vitamin B12 deficiency diagnosed.
Weglage (2000)	Germany	1 PKU (1F)	47y	Case report	- previously healthy female with bronchitis and a progressive neurological deterioration - mild spastic tetraparesis pronounced on the right side, ataxia, tremor, and severe concentration and anamnestic problems, cognitive deceleration, as well as disorientation. - Serum folate, vitamin B12 and CSF folate concentrations were normal.		882 umol/L on initial assessment 240 umol/L after introduction of low Phe diet	- Electroencephalography showed generalized slowing of the background activity, consistent with a generalized encephalopathy. - Somatosensory evoked potentials (SEP) of the median nerve and tibial nerve were normal, whereas the motor evoked potentials (MEP) were delayed for the right leg, but normal for the left leg and for the arms. - An alternating checkerboard pattern showed delayed VEP-P-100 latencies - the electroretinogram showed significantly decreased oscillating potentials. - Cranial MRI demonstrated severe white-matter abnormalities consistent with a dysmyelination in parieto-occipital, frontal and subcortical areas.

								- following introduction of a low Phe diet the patient made an almost complete recovery within 6 months. - the MRI still demonstrated changes of cerebral white matter, but only in the periventricular occipital area. - The patient demonstrated only very mild signs of residual ataxia and tremor. - Dysmyelination and reduced concentrations of the neurotransmitters dopamine and serotonin as consequences of elevated Phe levels may be causative factors.
Dericioglu (2010)	Turkey	I PKU (1F)	20y	Case report	- A 20y old female with PKU was admitted for uncontrolled seizures despite anticonvulsant treatment with LEV. - diagnosed with PKU at the age of 26 months, and therapy initiated at the age of 3 years,9 months. - first seizure at age 18y		Phe at time of seizure: 7.5 nmol/ml Phe at time of investigation: 125 nmol/ml	- Convulsions ceased after discontinuation of levetiracetam (LEV).and the patient has been seizure free on topiramate 125 mg/day.
Beckhauser (2011)	Brazil	1 ETPKU (1F)	19y	Case report	- clinical and neuroradiological aspects of a young adult diagnosed at birth with consistent control of Phe levels and good adherence to diet	N/A	120-360 µmol/l since 20 days of age	- despite continuous monitoring and early treatment, MRI identified abnormalities in the white matter – bilateral and symmetrical signs of demyelination.
Anwar (2013)	UK	1 ETPKU (1F)	41y	Case report	- medically retired nurse presented with subacute profound visual loss, cognitive dysfunction and paraparesis such that she was bed bound requiring full nursing care - unable to follow stage 1 commands consistently - diagnosed at birth and treated with a low Phe diet until 16y of age	16y	On presentation: 1564 umol/L (normal:120-480 umol/L) Following low Phe diet: 121 umol/L	- MRI of brain showed extensive abnormal gray matter and subcortical white matter within the frontal and parietal lobes with some atrophy. - meaningful functional improvement following reinstitution of a low Phe diet. - now independent in activities of daily living. - improvement in cognitive function, behaviour, visual and motor function.
Daelman (2014)	France	19 PKU (15 ETPKU) (9F/10M)	33-35y	Case reports Literature review case reports	- report of late onset neuropsychiatric symptoms in 4 PKU adults diagnosed in infancy and 1 diagnosed with PKU due to late onset neurological signs. - report clinical and radiological features and their evolution under diet therapy. - Literature review – 14 subjects, 11 diagnosed at birth, 4 diagnosis in adulthood	Mean age ceased diet: 12y (4.5-30y)	Mean Phe at neurological deterioration: 1475 umol/L (590-2000)	- the main neurological abnormalities in adult PKU patients were: brisk reflexes, spastic paraparesis, psychiatric signs that appear a mean of 10y (0-33y) after ceasing diet. - leukoencephalopathy occurred in 93% of cases on MRI scan. - 92% improved clinically after low Phe diet reintroduced. - high Phe levels (>1500umol/L were associated with neuropsychiatric signs.
Rosini (2014)	Italy	1 PKU (1F)	46y	Case report	- mild learning difficulties, presented with rapidly progressive dementia, walking difficulties and visual impairment that started at the end of 6-month unbalanced diet for slimming. - older sister, presenting with fair hair and skin (similarly to their unaffected mother), mental retardation and spastic tetraparesis, was diagnosed with PKU in infancy. - Patient's newborn screening was reported as negative.		947 umol/L on presentation 868 umol/L on low Phe diet	- physical examination disclosed fair hair with blue eyes. - Neurologic examination showed inability to walk, aphasia, prosopagnosia, extrapyramidal signs and brisk tendon reflexes. - Fundoscopy revealed pale optic disks. - Brain MRI evidenced diffuse bihemispheric white matter hyperintensity, mild cortical atrophy, and decreased N-acetyl-aspartate/creatine ratio at MR spectroscopy. - Electroencephalogram showed diffuse slowing of cerebral biorhythms. - Immediately after Phe-restricted diet with amino acid supplementation introduction, patient showed rapid improvement; 6

								months later (still under Phe restricted diet), only mild cognitive deficit and visual reduction remained, despite unvaried Phe levels. - One-year brain MRI and MR spectroscopy follow-up showed marked reduction of white matter abnormalities
Seki (2015)	Japan	1 PKU (1F)	48y	Case report	- female PKU patient presented with severe neurological symptoms more than 30 years after discontinuation of dietary treatment. - diagnosed age 6y. - difficulty walking and impaired speech, then bedridden and loss of consciousness.	15y	1380 µmol/L	- diagnosed as having neurological complications associated with PKU. - temporal changes in her laboratory data, brain MRI and single-photon emission computed tomography scan findings. - Brain MRI on T2-weighted, fluid-attenuated inversion recovery and diffusion-weighted images showed high intensity lesions in her bilateral frontal lobes and 123I-IMP SPECT showed marked and diffuse hypoperfusion in the bilateral cerebrum and cerebellum. - After the resumption of dietary treatment, serum Phe decreased to the reference target range. - neurological symptoms took longer to improve. - despite improvement in neurological dysfunction, white matter lesions continued to spread along the cerebral ventricles for several months. - SPECT abnormalities showed marked improvement after treatment.
Tufekcioglu (2016)	Turkey	1 male	59y	Case report	- admitted with blurred vision, cognitive problems, and gait difficulty that began 8 months before. - brisk reflexes and left side dominant parkinsonism.		Phe: 1075 µmol/L (normal 39–240 µmol/L)	- Mini-Mental State Examination score was 25/30, and neuropsychological evaluation showed a dysexecutive syndrome with simultanagnosia and constructional apraxia. - Clinical Dementia Rating score (CDR) was 1. - Cranial MRI showed bilateral diffuse hyperintense lesions in parietal and occipital white matter in T2, fluid attenuated inversion recovery, and diffusion weighted images. - Three months after Phe-restricted diet, his cognitive impairment and signs of parkinsonism significantly improved, with MRI scan unchanged.
Wang (2018)	China	1 male	21y	Case report	- presented with subacute leukodystrophy and visual-spatial disorders of late onset in adulthood. - delay in processing speed, declining mobility, autism, generalized apathy, and sometimes compulsion. - cranial MRI revealed brain leucodystrophy with symmetric abnormalities in bilateral deep cerebral white matter.		Before treatment Phe: 694 umol/L After diet treatment: 545 umol/L	- diagnosed with PKU overlapping homocysteine and folate deficiency. - treated with cobalamine, vitamin B6, folate and encouraged to follow a protein-restricted diet. - Visual disorientation and cognitive function showed improvement. - Head MR showed similar resolution with the original lesion. - Serum homocysteine and folate analysis were normal with decreased phenylalanine level.
Ashe (2019)	Australia	3 (2F/1M)	43y 47y 36y	Case reports	**Case 1:** diagnosed 12 mths, diet treatment from 18mths-9y. Restarted diet at 30y. Presented with attention deficits, hyperactivity, social and cognition issues, poor impulse control, anxiety, hallucinations particularly when blood Phe high.	9y 17y 7y	**Case 1:** poor diet control - Phe >1500 umol/L; good control 400-600umol/L **Case 2:** poor diet control - Phe 1200-	**Case 1:** when diet control good psychotic symptoms attenuated, anxiety minimal, impulse control normal. **Case 2:** at times of increased protein intake, there was increased mood lability, irritability, and anxiety with inattention and “cloudy” thinking. With improved diet control his mood lifted, anxiety reduced, sleep improved.

					Case 2: diagnosed at birth, strict diet control till 13y, relaxed diet to 17y. **Case 3:** diagnosed at birth, followed strict diet to 7y. Restarted diet at 35y due to symptomatic PKU affecting cognitive functioning and mental health – depression, mood swings, panic attacks, anxiety, self-harm. Difficulties with attention, concentration, memory, planning and organisation, slow mental processing. Unable to sustain employment.		1400 umol/L; good control <700 umol/L **Case 3:** poor diet control - Phe ~700umol/L; good control <300 umol/L	**Case 3**: after 12 months of good diet control (Phe<300umol/L) there was statistically significant improvements in psychomotor speed, planning and organisation, attention and self-monitoring. Also significant regression of white matter lesions. Depression and anxiety improved but still required some antidepressants.
Jaulent (2019)	France	8 PKU (6 ETPKU) (3F/5M) case reports 22 PKU (9 ETPKU) (9F/13M) case reports in the literature	18-50y	Case reports Literature Review	- neurological manifestations in 30 case reports of adult patients with PKU, associated with chronic or rapid increase of blood Phe, mostly when strict low-Phe diet was stopped early in life.	Mean age stopped diet: 15y (5-45y) Mean age onset of neurological symptoms: 32y (16-58y)	Mean Phe levels at time of neurological manifestation: 1500 µmol/L (840-2640) Mean Phe levels during diet: 640 umol/L (60-2410)	- Neurological symptoms consisted in cerebellar ataxia, tremor, brisk reflexes, visual loss, sensory manifestations, and/or headaches. - Visual loss was more frequent in the new cases (4/8) of the present series than in the literature (4/22). - neurological complications were associated with leucopathy on brain magnetic resonance imaging (27/29). - a low-Phe diet improved or fully reversed neurological manifestations, even in patients with late diagnosis during adulthood. - Neurological manifestations can complicate PKU in adult patients with elevated Phe levels, after long or short period of diet discontinuation.
Other studies								
Hanley (1993)	Canada	37 PKU (20F/17M)	Mean age: 21.6y (11-35y)	Cross sectional	- patients were monitored for evidence of vitamin B12 deficiency.			- mean haemoglobin 143g/L (106-170), mean MCV 91.7fL (81.9-113.8). - 6 patients (16%) had subnormal serum B12 (<150pmol/L) and 6 had borderline levels (150-200pmil/L). - 8 patients had MCV >94g/L, 3 had low or borderline serum B12. - 3 had low erythrocyte folate with low or borderline serum B12 as well.
McDonnell (1998)	UK	27 PKU (15F/12M)	Mean age: 26y (18-39y)	Cross sectional	- neurological history and examination, plasma Phe levels, pattern reversal visual evoked potentials, cortical and cervical somatosensory evoked potentials. - brain MRI (n=12).	Mean age stopped diet: 12y (1-22y)	Mean Phe: 1226 umol/L (280-2466)	- abnormal neurological features in 21/27 cases with significant delay of visual evoked potentials (63%) and somatosensory evoked potentials (14%). - periventricular white matter abnormalities in 5/12 patients who had MRI.
Robinson (2000)	UK	83 PKU 31 unrestricted diet 30 relaxed diet 22 strict diet	Median age: 22y (11-38y) Median age unrestricted: diet 22y Relaxed diet: 21y Strict diet: 24y	Cross sectional	- Neurologic examinations and dietetic assessment. - patients divided into 3 groups: strict, relaxed and unrestricted diet. - assays of blood samples were taken for vitamin B12 and folate and compared with the normal population.		Mean Phe Unrestricted diet: 1200 umol/L Relaxed diet: 1100 umol/L Strict diet: 500 umol/L	- vitamin B12 levels were significantly lower in the relaxed or unrestricted diet groups compared with the normal population. - folate levels were significantly elevated in all groups.

Koch (2002)	USA	73 ETPKU	30-35y	Longitudinal cohort	- follow-up study of adults who as infants were treated with a Phe -restricted diet to age 6y then randomized to continue or discontinue dietary treatment, 125 were followed until 10y of age, 98 until 12y. - 70 followed up as adults - medical, nutritional, psychological, genetic and socioeconomic assessments. - in a subset (n=21) of cases, magnetic resonance imaging and spectroscopy (MRI/MRS) were performed to study brain Phe concentrations (10 on continuous diet and 11 who discontinued before 10y of age).	4-8-6.5y (n=38) 6.5-12.5y (n=14) 12.5-20.0y (n=12) Never discontinued (n=9)	Mean Phe 6y: 826 umol/L 10y: 1627 umol/L Adult: 1448 umol/L 6y: 693 umol/L 10y: 1180 umol/L Adult: 1510 umol/L 6y: 686 umol/L 10y: 831 umol/L Adult: 1268 umol/L 6y: 558 umol/L 10y: 662 umol/L Adult: 926 umol/L	- subjects who maintained a phenylalanine-restricted diet reported fewer problems than the diet discontinuers, who had an increased rate of eczema, asthma, mental disorders, headache, hyperactivity and hypoactivity. - Psychological data showed that lower intellectual and achievement test scores were associated with dietary discontinuation and with higher childhood and adult blood Phe concentrations. - Abnormal MRI results were associated with higher brain Phe concentrations. - Early dietary discontinuation for subjects with PKU was associated with poorer outcomes not only in intellectual ability, but also in achievement test scores and increased rates of medical and behavioural problems.
Brumm (2004)	USA	24 ETPKU (11F/13M)	Mean age 29y (21-32y)	Cohort	- examined a group of early-early treated adult subjects with PKU for neuropsychological deficits to determine: (1) pattern of cognitive dysfunction; (2) whether subjects with high concurrent blood phenylalanine performed worse on cognitive tests; and (3) specific treatment variables that may be associated with cognitive difficulties in adulthood. - historical and current blood Phe levels. - Neurological assessments for attention, executive function, learning and memory, language functioning, visual perceptive skills, emotional adjustment, psychomotor speed and fine motor coordination.	Mean 15y (5-31y)	Mean: 6y: 702 umol/L (321-1562) 10y: 1049 umol/L (194-1786) Adult: 1184 umol/L (255-2420) Current: 1038 umol/L (157-1723)	- Results suggest that adults with early-treated PKU demonstrated specific cognitive deficits - Deficits were noted in several domains including executive functioning, attention, verbal memory, expressive naming and verbal fluency. - those with a concurrent Phe level >1000 mmol/L scored lower than those with a Phe level<1000 mmol/L on a number of cognitive tasks including focussed attention, verbal fluency, reaction time, verbal recognition memory, visual memory and naming. - Variables related to language functioning were negatively correlated with blood Phe level across the lifespan, and positively correlated number of years on diet. - in spite of early dietary treatment and normal IQ, adults with PKU show deficits in cognitive functioning. - the group as a whole performed well below expectation on a verbal learning and memory task including immediate recall, incidental learning over five trials, short- and long-delayed recall and recognition memory. - Other areas of cognitive weakness included visual memory, verbal fluency, expressive naming and selective executive skills.
Feldmann (2005)	Germany	35 ETPKU 35 age/gender matched Diabetics	Mean age: 17.8y (13-21y)	Case-control	- long-term study to determine whether adolescents and young adults with PKU show frontal lobe-dependent deficits when compared to diabetic patients. - assessed for IQ, information processing, and selective and sustained attention. - assessments repeated within a 3-year follow-up.		Mean Phe at baseline: 906 umol/L (72-1716) Mean Phe at 3 year assessment: 822 umol/L (252-869)	- PKU patients showed no increase in blood phenylalanine concentrations at follow-up but had significantly poorer test results than the diabetic patients at both assessment times. - PKU group showed poorer performance speed. - Elevated phenylalanine concentrations seem to exert a global effect slowing performance speed.

							Mean lifetime Phe (at baseline): 528 umol/L (269-869) Mean lifetime Phe (at follow-up): 573 umol/L (198-902)	
Moyle (2007)	Australia	12 ETPKU (12F/2M) 12 non-PKU matched controls	Mean PKU age: 28.5y Mean control age: 29.2y	Case-control	- tests administered included the Wechsler Adult Intelligence Scale-III (WAIS-III) (Psychological Corporation, 1997), the Wechsler Memory Scale Third Edition (WMS-III; Psychological Corporation, 1997), and executive function measures (the Trail Making Test and the Controlled Oral Word Association Test). - lifetime and current plasma Phe levels.	All on unrestricted diet at time of testing		- reduction in the Perceptual Organization Index (POI), Processing Speed Index from the Wechsler Adult Intelligence Scale Third Edition, and Part A of the Trail Making Test for the PKU group relative to controls. - From the WAIS-III index scores, POI correlated significantly with plasma Phe at time of assessment. - Index scores from the WMS-III: mean plasma Phe at assessment correlated significantly with all of them, except for Working Memory. - Executive function tests: significant correlation between mean plasma Phe at baseline and Part B of the Trail Making Test - These results supported a profile of reduced information-processing speed in adults with PKU.
Didycz (2017)	Poland	25 ETPKU (18F/7M)	Mean age: 15y (13-17y)	Cross sectional	- teenagers with ETPKU, continuous follow-up, normal intellectual development, and treatment adherence problems (at least 25% of the results of blood Phe tests exceeding the recommended limit of 360μmol/L). - every patient was assessed with The State-Trait Anxiety Inventory, an introspective psychological inventory consisting of 40 self-report items pertaining to anxiety that distinguishes between a person's state and trait anxiety levels. - recent and lifetime mean blood Phe levels and frequency of measurements as a measure of treatment adherence.		Mean lifetime Phe: 510 umol/L (280-770) Mean Phe on the day of assessment: 690 umol/L (120-1460) Mean no. tests/year: 11 (6-18)	- demonstrated significant correlations of anxiety with variability of blood phenylalanine concentrations and with severity of hyperphenylalaninemia. - there were moderate-to-strong correlations between lifetime mean blood Phe concentrations and recent blood Phe levels and A-Trait scores. - Avoiding blood Phe fluctuations in childhood can probably reduce anxiety in adolescents with PKU.
ten Hoedt (2010)	Netherlands	9 ETPKU (6F/3M) 9 non-PKU controls	Mean age: 23.6y (19-34y)	Randomised double-blind placebo-controlled crossover	- effects of short-term elevation of Phe levels on neuropsychological functions and mood of adults with PKU. - two 4-week supplementation periods: one with Phe, mimicking normal dietary intake, and one with placebo in randomly allocated order in a double-blind cross-over design. - a set of neuropsychological tests		Mean pre-study Phe: 649 umol/L (346-978) Mean Phe in Phe loading phase: 1259 umol/L Mean Phe in placebo phase: 709 umol/L	- Mean plasma Phe was significantly higher during Phe supplementation compared with placebo. - Neuropsychological tests demonstrated an impairment in sustained attention during Phe supplementation. - Both patients and their friend or relative reported lower scores on the mood questionnaires during Phe supplementation. - short-term high plasma Phe levels have a direct negative effect on both sustained attention and on mood in adult patients with PKU.

					was administered at the end of each study period. - patients and for each patient a friend or relative, completed weekly Profile of Mood States questionnaires. - Phe levels were measured twice weekly.			
Anjema (2011)	Nether lands	48 ETPKU (22M/26F)	0-35y (8.5y)	Observational interview (blinded)	- current blood Phe concentrations - questionnaire by interview regarding hyperactivity, mood swings, introvert/extrovert behaviour - blood Phe and questionnaire repeated in each subject 3-37 times (median: 8). - interviewer and patient blinded to blood Phe levels	N/A	Median Phe concentrations in patients >12 years: 558 µmol/l (221–1171) <12y: 238 µmol/l (89–521)	- positive association between high Phe concentrations and mood swings.
Nardecchia (2015)	Italy	14 ETPKU (12F/2M) 14 non-PKU matched controls	Mean age PKU 1st assessment: 10.8y (7.8–13.5y) Mean age PKU 2nd assessment: 25y (22.2–27.7y) Mean age controls: 23.7y (21-28y)	Longitudinal cohort	- assessed for IQ and neuropsychological functioning including executive functions (EF) over 14 years of follow-up.			- Compared to control subjects, mean IQ of patients was significantly lower, particularly in those with poorer control (Phe >600umol/L). - All patients that underwent a second MRI scan showed white matter alterations ranging from mild to severe. - Cognitive, neuropsychological and neuroimaging outcome was influenced by life-long and/or second decade of life metabolic control. - suboptimal neurocognitive outcome despite an overall improvement of neuropsychological functioning, was associated with the worsening of metabolic control. - performances of patients with a good life-long metabolic control were not significantly different from control subjects in all tasks.
Prochazkova (2015)	Czech Republic	29 PKU (15 adult) 22 HPA (8 adult)	3-48y	Prospective cross sectional	- to determine the incidence of vitamin B12 deficiency in patients with phenylketonuria (PKU) and hyperphenylalaninemia (HPA), and its associations with B12 vitamin parameters (holotranscobalamin – active vitamin B12, serum folate, total plasma homocysteine, and plasma methylmalonic acid concentration).		Mean PKU Phe: 357 umol/L (102-1144) Mean HPA Phe: 309 umol/L (188-454)	- A significant difference in serum folate levels was observed between adult HPA patients and PKU patients. - A significant difference in plasma homocysteine concentrations within the normal levels was detected between adult HPA and PKU patients. - adults also had significant differences in serum holotranscobalamin concentrations - adult patients with PKU and HPA are at risk of vitamin B12 nutritional deficiency.
Bilder (2016)	USA	82 primary studies (42 noninterventional; 40 interventional – blinded crossover, cohort, case reports)		Systematic Review/ Meta-analysis	- investigates the impact of elevated blood Phe on neuropsychiatric symptoms in adults with PKU. - studies assessing effects of reducing blood Phe for ≥3 weeks in adults with PKU and neuropsychiatric symptoms: (n=10 studies; 253 subjects). - Studies assessing effects of blood Phe on executive function in adults with PKU: (n=9 studies; 253 subjects) - 10 studies reporting psychiatric symptoms in adults with PKU including prevalence of			- neuropsychiatric symptoms associated with PKU exceed general population estimates for inattention, hyperactivity, depression, and anxiety. - high Phe is associated with an increased prevalence of neuropsychiatric symptoms and executive functioning deficits. - low Phe is associated with improved neurological performance. - 20 adults with PKU had late-onset neurologic symptoms (11 cases of spastic paraparesis/ quadriplegia, 3 cases of muscle weakness/difficulty walking, 3 cases of vision loss) and/or psychiatric symptoms (3 cases of disabling depression, 4 cases of communication difficulty, 1 case of agoraphobia). Reducing blood Phe resulted in marked improvement of symptoms in 13 of 20 cases.

					inattention, hyperactivity, anxiety or depression. - 10 studies reporting neurologic symptoms including prevalence of epilepsy/seizures and tremors.			In additional 8 adults with PKU, intellectual disability, and severely disruptive behaviour, 7 adults showed marked reduction in disruptive behaviours on a Phe-restricted diet. - four studies used a single cohort intervention approach and found improvements with reduced Phe on reaction time (1 study), attention (3 studies), and cognitive flexibility (1 study). - five studies compared an on-diet (or low Phe) cohort with an off diet (or high Phe); better scores were associated with on-diet and/or low Phe in two or more studies for attention, working memory, and psychomotor speed/reaction time. - one study plotted test results for working memory (Spatial Working Memory test), attention (Rapid Visual Information Processing test), and inhibitory control (Stop Signal Task) as a function of blood Phe level in 50 patients with classic PKU. Plots demonstrated a visual trend of increasing executive function deficits with increasing blood Phe levels. - 7/7 cohort intervention studies reported neuropsychiatric improvement upon resumption of Phe-restricted diet. - meta-analysis results show higher than expected rates for neuropsychiatric comorbidity compared with the general population, even among early-treated PKU. - Executive functioning impairment impacts daily life by interfering with the ability to perform basic cognitive tasks such as focusing, memory, planning and impulse control.
Bilder (2017)	USA	3714 ETPKU (62%M/38%F) and 22,726 age/gender matched general population controls (60%M/40%F) and 7060 age/gender matched subjects with diabetes mellitus (62%F/38%M)	20-80+y Mean age: 39y ETPKU 38y Diabetes 41y controls	Retrospective cohort Case-control	Neuropsychiatric diagnoses were assessed including attention-deficit hyperactivity disorder (ADD/ADHD), alcohol dependency, anxiety, autism spectrum disorder, bipolar disorder, depression, eating disorder, epilepsy and convulsion, fatigue and malaise, intellectual disability, migraine and headache, movement disorders, Parkinson's, tremor, obsessive-compulsive disorder (OCD), pain disorder, personality disorder, and Tourette syndrome/tic disorder.			- The PKU cohort experienced significantly higher rates of comorbid neurologic, psychiatric and developmental conditions compared to the general population: intellectual disability, autism spectrum disorder, Tourette/tic disorders, and eating disorders. - Rates of fatigue/malaise, epilepsy/ convulsions, sleep disturbance, personality disorders, phobias, psychosis, and migraines among those with PKU exceeded rates for the general population but were comparable to those with diabetes. - In those aged 20-39y, prevalence ratio is significantly higher for 19/24 neuropsychiatric and neurocognitive comorbid conditions compared with controls. - anxiety was higher in PKU than in controls or diabetes. - depression was higher in PKU than in controls but comparable to diabetes.
Boot (2017)	Nether lands	18 ETPKU (9F/9M) 12 controls (7F/5M)	Mean age PKU: 31y (18-42y) Mean age control: 27y (20-39y)	Case-control	- 2 day dietary record, - Venous blood sample for plasma monoamine metabolite and blood amino acid levels. - protein magnetic resonance spectroscopy scan to assess brain Phe levels. - executive function tasks & impulsivity questionnaire. - hypothesis that adults with PKU have higher striatal dopamine D2/3		706.8 ± 347.1 µmol/l blood Phe 42.2 ± 17.1 µmol/l blood Tyr	- Self-reported impulsivity levels were significantly higher in PKU patients compared with healthy controls. - significantly higher striatal D2/3R availability in adult PKU patients in comparison with control participants, suggesting that there may be reduced concentrations of dopamine in the synapse. - there was significant positive correlation between striatal D2/3R availability and error rate on a cognitive flexibility task in the adults with PKU.

					receptor (D2/3R) availability with [123I]iodobenzamide (IBZM) single-photon emission computed tomography (SPECT), as a proxy marker of a reduced brain synaptic dopamine concentration, and lower peripheral monoamine metabolite levels, relative to healthy controls; also that adults with PKU demonstrate relationships between D2/3R availability with brain and blood Phe levels, and with self-reported levels of impulsivity and neurocognitive performances.			
Jahja (2017)	Nether lands	21 PKU (15F/6M)	Mean age at childhood assessment: 10.4y (6.9-13.7) Mean age at adult assessment: 25.8y (21.0-30.5)	Cohort	- executive functioning (EF) was assessed during childhood (T1), and again in adulthood (T2). - At T2 additional assessments of EF in daily life and mental health were performed.		Mean Phe in childhood: 330µmol/L (219–581) Mean Phe at T2: 464µmol/L (276–743)	- Childhood (0–12y) blood Phe was significantly related to cognitive flexibility, executive motor control, EF and mental health in adulthood. - Patients with a greater increase in blood Phe >12y performed more poorly on EF-tasks at T2. - patients with blood Phe <360 µmol/L in childhood and ≥360 µmol/L from age 13 onwards (n = 11) had better cognitive flexibility and executive motor control than those who had Phe ≥360 µmol/L throughout life (n = 7).
Jahja (2017)	Nether lands	57 ETPKU (33F/24M) (12 BH4 responsive) 57 non-PKU matched controls	Mean age: 27.7y (18-40y)	Case-control	- cognitive profile and mental health in adult PKU, in relation to Blood Phe and BH4 treatment. - performed IQ subtests and executive function tests and the Adult Self-Report on mental health problems. - subset of BH4 vs non bh4 users, matched for childhood Phe level.		Mean concurrent Phe non-BH4: 699 umol/L (66–1550) BH4: 489 umol/L (220–1030) Mean lifetime Phe Non-BH4: 505 umol/L (253–1001) BH4: 348umol/L (223–527) Mean childhood Phe Non-BH4: 372 umol/L (181–903) BH4: 302 umol/L (181–689) Controls: 25.7 umol/L (18.1–40.8)	- Patients with PKU had normal IQ although lower than controls. - They performed poorer on working memory, inhibitory control, and sustained attention tasks. - Patients reported depressive and avoidant personality problems more frequently. - patients with childhood and lifetime phenylalanine >360umol/L had poorer cognitive and mental health outcomes than controls. - comparisons between patients on and off BH4 showed that non-BH4 users were slower (on number of tasks) and reported more mental health problems.
Palermo (2017)	UK	37 ETPKU (13M, 24F) 30 age matched controls (10M/20F)	Mean age 27.5y (SD 7.3)	Case-control	- Blood Phe - IQ – vocabulary, block designs, similarities, matrix reasoning - visuospatial attention - visuomotor coordination	7 patients on unrestricted diet, 30 on low Phe diet in adulthood	- Mean blood Phe in adolescence and adulthood and current levels are all correlated with level of impairment	- IQ significantly lower in PKU compared with controls - 46% PKU had an abnormal cognitive profile, significantly more so than controls - 24% PKU had clear cognitive impairment

					- complex executive function –attention, verbal/ visual memory & learning		- reaction times particularly sensitive to blood Phe concentrations	- visuospatial attention, visuomotor coordination, speed of processing and complex executive functions are particularly impaired - impairments in reasoning, planning and monitoring - significant cognitive impairments even in those with better metabolic control
Romani (2017)	UK	37 ETPKU (24F/13M) 30 non-PKU age and gender matched controls (20F/10M)	Mean PKU age: 27.5y Mean control age: 27.6y	Case-control	- tasks – IQ (WASI), speed of processing measures (visuo-spatial attention, language processing), visuomotor coordination, higher order executive functioning, inhibitory control, sustained attention, short-term memory.	n=30 still on diet n=7 unrestricted diet	Mean Phe in childhood: 452umol/L Mean Phe in adolescence: 714umol/L Mean Phe in adulthood: 787 umol/L Mean lifetime Phe: 690 umol/L Current Phe: 720 umol/L	- ETPKU patient performance could be explained by: (a) a deficit in the allocation of visuo-spatial attention that reduced speed in visual search tasks, in some reading conditions and visuo-motor coordination tasks; and (b) a more conservative decision mechanism that slowed down returning an answer across domains. - These results suggest that the impairments in executive functions seen in ETPKU are not the consequence of a generalized speed deficit.
DeFelice (2018)	UK	38 ETPKU (25F/13M) 38 non-PKU controls (29F/10M)	Mean age: 27y	Case-control	- an in-depth analysis of language functions in early-treated adults with PKU as compared to age- and education-matched controls. - tasks: narrative recall, blocked cyclic naming, prosody, pragmatics, lexical inhibition, strategic planning.	31 still on diet, 7 off diet	Mean Phe at age 0-10y: 429 umol/L Mean Phe at age 11-16y: 675 umol/L Mean Phe at age 17+y: 751umol/L Mean Phe at time of verbal narrative testing: 689umol/L Mean Phe at time of pragmatic tasks: 794 umol/L	- Patients with PKUs had intact basic language processing but had deficits in planning and reasoning abilities. - Compared to controls, PKUs were: less informative in narrative production; slower in metaphorical understanding and inferred meaning; less accurate in focused lexical-search. - These results suggest that i) executive deficits in PKU cannot be explained by an accumulation of lower-order deficits and/or general speed impairments, ii) executive functions engage dedicated neurophysiological resources, rather than simply being an emergent property of lower-level systems.
Feldmann (2019)	Germany	35 ETPKU (22F/13M) 18 age matched non-PKU controls (7F/11M)	Mean PKU age: 41y (29-51y) Mean control age: 44y (30-54y)	Cohort	- to assess the neurological and neuropsychological outcome in adult patients with early-treated PKU. - assessed for their intelligence quotient (IQ), attention and information-processing abilities. - MRI brain scan. - Neuropsychological assessments and MRI were repeated at five and ten-year follow-up			- At both follow-up assessment times the IQ scores were significantly lower in PKU compared to controls. - Older adult patients (> 42 years) showed poorer information processing and attention at both assessment times compared to younger adult patients and controls. - IQ was significantly correlated to blood Phe in patients' childhood and adolescence, and Phe levels had been higher in the adolescent years of older adult patients.

								- Neuropsychological assessment in adults with PKU showed neurocognitive impairment particularly in older adult patients. -
Pilotto (2018)	Germany	10 ETPKU 15 (8F/7M) age matched non-PKU controls	Mean PKU age: 38.2y (30-45y) Mean age controls: 35y	Case-control	- Plasma and cerebrospinal fluid (CSF) Phe, 5-hydroxyindoleacetic acid (5-HIAA), 5-hydroxy-tryptophan (5-HTP), 3,4-dihydroxy - L-phenylalanine (L-DOPA) and homovanillic acid (HVA) were analyzed. - Voxel-based morphometry statistical nonparametric mapping was used to test the age-corrected correlation between gray matter atrophy and CSF biogenic amines levels.	n=4 of diet Mean age stopped diet: 28y (19-40y)	Mean Phe: 782 umol/L (57-1115)	- Significant negative correlations were found between CSF 5-HIAA, HVA, and 5-HTP and Phe levels. - A decrease in 5-HIAA and 5-HTP concentrations correlated with precuneus and frontal atrophy, respectively. - Lower HVA levels correlated with occipital atrophy. - Biogenic amines deficits correlate with specific brain atrophy patterns in adult PKU patients, in line with serotonin and dopamine projections. - The study shows that serotonin and to a lesser extent dopamine metabolite are reduced in adult PKU patients and correlate with specific GM atrophy patterns.
Romani (2019)	UK Italy	56 ETPKU (35F/21M) (19 Italian, 37 UK) 49 non-PKU age matched controls (28F/21M) (19 Italian, 30 UK)	Mean PKU age: 26.8y Mean control age: 26.5y	Case-control	- The objective was to investigate which metabolic variables are most important for predicting cognitive outcomes (Phe average vs Phe variation) and assessing the risk of cognitive impairment associated with a more relaxed approach to the diet than is currently recommended. - associations between metabolic and cognitive measures in a mixed sample of English and Italian early-treated adults with PKU. - Metabolic measures were collected through childhood, adolescence and adulthood; cognitive measures were collected in adulthood. - Metabolic measures included average Phe levels and average Phe variations. - Cognition was measured with IQ and a battery of cognitive tasks.		Medan childhood Phe: 457 umol/L Phe fluctuation: 214umol/L Median adolescent Phe: 714 umol/L Phe fluctuation: 162umol/L Median adult Phe: 859 umol/L Phe fluctuation: 164 umol/L Median Lifetime Phe: 655 umol/L Phe fluctuation: 179umol/L Current Phe: 833umol/L (65-2081)	- Phe variation was as important as Phe average in predicting adult outcomes and contributed independently. - Together, childhood Phe variation and adult Phe average predicted around 40% of the variation in cognitive scores. - Poor cognitive scores (>1 SD from controls) occurred almost exclusively in individuals with poor metabolic control and the risk of poor scores was about 30% higher in individuals with Phe values exceeding recommended thresholds. - results provide support for current European guidelines (average Phe value = < 360 µmol/l in childhood; = < 600 µmo/l from 12 years onwards), but they suggest an additional recommendation to maintain stable levels (possibly Phe SD = < 180 µmol/l throughout life). - avoiding blood Phe peaks was as important if not more important that maintaining average low Phe levels, particularly in childhood. - blood Phe levels above recommended European guidelines were associated with around 30% increase in the risk of poor cognitive outcomes.
Aldridge (2020)	USA	20 ETPKU (11M/9F) 20 age matched non-PKU controls (10M/10F)	11-27y (16y)	Case-control	- MRI brain images - whole brain volume, whole cerebellum volume, cerebellar gray matter volume, and cerebellar white matter volume - blood Phe concentrations – mean lifetime, last 12 months, last 3mths	N/A	- significant association with whole brain volume and dietary treatment adherence as reflected by higher lifetime blood Phe, mean Phe over the last year, or over the last 3mths	- significant reduction in cerebellar gray matter volume observed for PKU group compared to controls. - consistent with the hypothesis that the cognitive difficulties experienced by individuals with PKU may be related to disruptions in gray matter. - trend for age related (<16y vs >16y) decrease in whole cerebellar volume & cerebellar white matter in PKU group but not in controls.

Boulet (2020)	France	151 PKU (97F/54M) from 17 metabolic centres	Mean age: 27y (18-45y)	Cross-sectional	- similarities between tryptophan (Trp) and Phe metabolisms exist so it may be that a modification of Trp metabolism in PKU might be responsible for some neurological impairment, not just blood Phe concentrations. - Plasma Trp, kynurenine (KYN), 3-hydroxykynurenic acid (3HK) and kynurenic acid (KA) were analysed. - evaluations of cognition, behaviour, QoL questionnaires and dietary assessment.		Mean on diet and AA: 982 umol/L (15-1938) Mean on diet only: 1243 umol/L (661-1900) Mean off diet: 1235 umol/L (156-2328)	- KYN and 3HK were significantly lower and KA was significantly higher in patients with PKU compared to general population. - 3HK concentration was significantly different between PKU patients on controlled low-Phe diet compared to PKU patients not on diet but still not at the same level as in the general population. - Trp metabolism is modified in adult PKU patients.
Clocksin (2021)	USA	22 ETPKU (9F/13M) 21 non-PKU controls (8F/13M)	Mean age PKU: 21y (9-35y) Mean age controls: 21y (9-33y)	Case-control	The Wechsler Abbreviated Scale of Intelligence was administered to all participants. Scores for the ETPKU group ranged from 75 to 122 (M = 98.0, SD =12.3), and were significantly lower than scores for the non-PKU group 89 to 128 (M=111.2, SD=8.0). - Automated Fibre-Tract Quantification (AFQ) was used to investigate tract-specific patterns of change in brain white matter (WM) abnormalities. - Diffusion Tensor Imaging (DTI) data was analyzed using AFQ. - a subsample of 8 individuals with ETPKU was re-evaluated 6 months later after demonstrating a significant reduction in blood Phe levels following initiation of BH4 treatment.		Mean phe in previous year: 778 umol/l (138-1398) Mean Phe in previous month: 776 umol/L (238-1398) BH4 subset: Mean Phe pre-treatment: 693 umol/L (260-1049) Post-treatment Phe: 375umol/L (145-702)	- Within-tract AFQ analyses revealed significant location-by-group interactions for several WM tracts throughout the brain. - In most cases, ETPKU-related disruptions in mean diffusivity (MD)were more apparent in posterior (as compared to anterior) aspects of a given tract. - Reduction in blood Phe levels in a subset of patients taking BH4 was associated with a similar pattern of improvement (posterior-to-anterior) within most tracts. - Findings suggest that there is a systematic pattern of change in WM abnormalities in individuals with ETPKU in a posterior-to-anterior manner along individual WM tracts. - increased Phe levels are associated with more pronounced WM abnormalities, especially in more posterior aspects of the cortical WM tracts. - ETPKU-related differences in MD were also observed in ventral aspects of the right corticospinal tract, suggesting possible brainstem level involvement.
Pilotto (2021)	Italy Germany	19 (12F/47) ETPKU 19 (15F/4M) age and gender matched controls	Median PKU age: 41y (35-44) Median Control age: 34y (30-40y)	Prospective cross sectional	- extensive neurological evaluations, neuropsychological and behavioural testing, sensory and motor evoked potentials and MRI. - CSF concentrations of neurodegenerative markers were additionally evaluated in a subset of 10 patients.	>18y	Median PKU Phe: 873 umol/L (644-1115) Median control Phe: 44 umol/L (38-50)	- patients with PKU showed higher prevalence of neurological symptoms, cognitive and behavioural abnormalities, autonomic dysfunction, alterations in neurophysiological measures and atrophy in putamen and right thalamus compared to controls. - plasma Phe levels highly correlated with the number of failed neuropsychological tests, neuropsychiatric symptoms, motor evoked potential latency and parietal lobe atrophy. - in CSF patients with PKU exhibited higher amyloid and Tau pathology. - strong evidence for a correlation between Phe levels and clinical, neuropsychological, neurophysiological, biochemical and imaging alterations in adult phenylketonuria patients.
Burgess (2021)	Australia	9 ETPKU (5F/4M)	Mean age: 33y (19-47y)	Prospective cohort	- re-initiated dietary control for ETPKU patients and monitored cognitive and psychiatric outcomes over a twelve-month period. - assessments included objective cognitive function (measured by cognitive proficiency index (CPI)), anxiety and depression scales.	Mean time off dietary control: 19y (5-30y)	Mean baseline Phe: 1108 umol/L (728-1602)	- general linear mixed model analysis demonstrated a positive relationship between cognitive proficiency index and time on diet. - there was a negative relationship between time on diet and anxiety and depression ratings.

ETPKU = Early treated PKU, diagnosed shortly after birth, with diet treatment implemented

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4. UNTREATED ADULTS WITH PKU AND INEQUALITY OF ACCESS TO TREATMENT

Previously untreated adults with PKU should also be considered for sapropterin treatment. There are many late diagnosed and untreated patients with PKU who were either born prior to newborn screening, failed newborn screening in the 1960's or have immigrated from countries without newborn screening or treatment. Untreated patients with severe intellectual disability and challenging behavioural problems have high support needs, and some may live in social care homes or with very elderly relatives. Interventions to lower blood phenylalanine levels may be beneficial. There is evidence from case studies and cohort studies that dietary treatment may reduce aggressive behaviour, self-injury, hyperactivity, restlessness, irritability, sleep disorders, and anxiety. It improves mood, social interactions, verbal communication, and daily living skills. It also improves attention span, alertness, short-term memory processes, motor skills, seizures, spasticity, and tremors. It will reduce

nursing time, use of sedatives, anti-psychotic, anticonvulsants; it will also improve eczema and body odour. Unfortunately, many care homes are unable to cope with dietary treatment due to the time it takes to prepare suitable food and supervise that it is given appropriately. This vulnerable group of patients should be given equal opportunity to see if they are sapropterin responders as this treatment could improve their quality of life considerably without the need for strict dietary treatment. It will also ease the burden of care on health and care services.

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5. MATERNAL PKU AND EVIDENCE TO SUPPORT THE NEED FOR SAPROPTERIN DURING PRE-CONCEPTION AND POST NATALLY

- Achieving a healthy pregnancy outcome in women with PKU is strongly influenced by their blood phenylalanine control throughout pregnancy as well as their health status and diet.

- High blood phenylalanine levels during pregnancy have a teratogenic effect on the developing foetus that causes growth retardation, microcephaly, intellectual disabilities, and birth defects, including congenital heart defects (CHD). A summary of reported effects of poor blood phenylalanine control in maternal PKU is given in table 5. Generally, the longer blood phenylalanine levels are out of metabolic control, the worse the foetal outcome. Control of maternal blood phenylalanine during

pregnancy prevents most if not all of these complications (Lenke and Levy 1980; Rohr et al. 1987; Koch et al. 2003). Children born to mothers with PKU who attain satisfactory blood phenylalanine control before pregnancy are comparable to the normal population.

- It is recommended that woman with PKU should follow a strict low phenylalanine diet prior to pregnancy/pre-conception as features of maternal PKU syndrome are preventable by starting a low phenylalanine diet before conception. The time to reach stable and acceptable blood phenylalanine concentrations varies between women. It is influenced by personal conditions (organizational skills, IQ, work conditions) and family support, which will affect the ability to adhere to strict long-term diet.

- Evidence has proven that sapropterin lowers blood phenylalanine in BH4 responsive patients with PKU. Thereby, there is no reason why it should not lower blood phenylalanine levels during the pre-conception period and pregnancy in BH4 responsive women (see later discussion).

- About half of pregnancies in maternal PKU in the UK are accidental. This is similar to national figures for non PKU pregnancy. This means at the time of conception; maternal blood phenylalanine levels are likely to be higher than target ranges. Furthermore, some women may delay seeking advice once they know they are pregnant due to fear and guilt leading to further delay before stringent diet therapy is commenced. Young women, those with lower education and living on income support are the most vulnerable and are more likely to experience accidental pregnancy. Furthermore, women with disability are less likely to use reliable contraception and are particularly at risk (Holdsworth et al 2018). *Holdsworth E, Trifonova V, Tanton C, Kuper H, Datta J, Macdowall W, Mercer CH. Sexual behaviours and sexual health outcomes among young adults with limiting disabilities: findings from third British National Survey of Sexual Attitudes and Lifestyles (Natsal-3). BMJ Open. 2018 Jul 5;8(7):e019219.*

- Maternal delay in attainment of acceptable blood phenylalanine control is associated with decline in their child's developmental outcome/IQ score. Waisbren and Azen (2003) conducted a prospective longitudinal study that assessed cognitive and behavioural outcomes in children from women with PKU. Two hundred and twenty-eight children who were born to mothers with treated PKU or untreated mild hyperphenylalaninemia were compared with 70 control subjects at 7 years of age. They found that the children's cognitive outcome negatively correlated with the number of gestational weeks that elapsed until maternal metabolic control was achieved. There was an increased risk of low IQ in the children if the mother came from a lower socio-economic background and was also unable to provide a stimulating early home environment. The postnatal environment also significantly affected outcome. *Waisbren SE, Azen C. Cognitive and behavioral development in maternal phenylketonuria offspring. Pediatrics. 2003 Dec;112(6 Pt 2):1544-7.*

- In a separate study, Waisbren followed up 57 children from 24 mothers with PKU. The children ranged in age from 1 month to 26 years with 21 (62%) over 6 years. The mean IQ of children was 94, with 12% performing in the range of intellectual disability (IQ < 70). Among children >5 years of age, 25% had learning disabilities,

31% had attention deficit hyperactivity disorder (ADHD), 22% were on ADHD medication, and 34% had a diagnosis of anxiety and/or depression. *Waisbren SE, Rohr F, Anastasoaie V, Brown M, Harris D, Ozonoff A, Petrides S, Wessel A, Levy HL. Maternal Phenylketonuria: Long-term Outcomes in Offspring and Post-pregnancy Maternal Characteristics. JIMD Rep. 2015;21:23-33.*

- Widaman demonstrated a threshold effect of a mother's mean blood phenylalanine of 400 µmol/l in relationship to their child's IQ. With every further increase of 60 µmol/l Phe, the IQ decreased by 4.7 points in their infant. *Widaman KF. Phenylketonuria in children and mothers: genes, environments, behavior. Curr Dir Psychol Sci. 2009;**18**(1):48.*

- In the UK, there is no current registry describing child/foetal outcome following maternal PKU pregnancy. However, in 2008, Maillot et al conducted a retrospective review of outcomes in 105 children born to mothers with PKU in the UK. They found that IQ and developmental quotient (DQ) at age 1 and age 8 were higher in children whose mothers started a low phenylalanine diet before pregnancy compared with those whose mothers started the diet after pregnancy began, at a mean gestational age of 10 weeks. Starting the diet before the beginning of pregnancy also reduced the risk of CHD (0% for the prior-to-pregnancy diet group vs. 12.5% for the group initiating diet 10 weeks after pregnancy began). *Maillot F, Lilburn M, Baudin J, Morley DW, Lee PJ. Factors influencing outcomes in the offspring of mothers with phenylketonuria during pregnancy: the importance of variation in maternal blood phenylalanine. Am J Clin Nutr. 2008 Sep;88(3):700-5.* There is also evidence of other poor outcome of maternal PKU in the UK (see Table 5 for maternal PKU studies describing outcome).

- Poor maternal nutrition in pregnancy is also associated with worse outcome. Congenital heart disease is higher when women are eating a poor quality diet particularly if they consume a low protein, low fat and low vitamin B12 intake. The use of sapropterin will increase the intake of these nutrients in BH4 responsive women. *Michals-Matalon KMR, Acosta P, Azen C. Congenital heart disease in maternal phenylketonuria: effects of blood phenylalanine and nutrient intake. MRDD Res Rev.1999;**5**:121–124*

- Most women with maternal PKU find a strict low phenylalanine diet particularly difficult in the pre-conception period. Some women even chose not to have children due to concern and fear about their ability to cope with pregnancy. *Ford S, O'Driscoll M, MacDonald A. Reproductive experience of women living with phenylketonuria. Mol Genet Metab Rep. 2018 Nov 2;17: 64-68*

- Data from case studies (Table 5) suggests that sapropterin is safe in pregnancy and will lower blood phenylalanine concentrations in sapropterin responsive women. Prescription of sapropterin to responsive women in the pre-conception period may lessen the time required to achieve acceptable blood phenylalanine control prior to pregnancy. It should help improve nutritional status. During pregnancy it should enable women to eat more natural protein so they are less reliant on artificial nutrition; this should improve the quality of blood nutrient supply available to the infant. In addition, administration of sapropterin in combination with dietary treatment in the post-natal period may help women maintain blood phenylalanine

control within acceptable limits, assist women to sustain breast feeding by helping them eat sufficient calories, and lessen any PKU related symptoms due to poor metabolic control.

- There is a current NHS policy that suggests that sapropterin can be prescribed only when women demonstrate they are unable to achieve lower blood phenylalanine levels in pregnancy. At this point women may be several weeks pregnant and no prior BH4 responsive test will have been conducted. This policy is only allowing sapropterin to be being used as a type of 'rescue therapy' when the clinical situation is particularly difficult and BH4 responsiveness has not been proven. This is inappropriate and this practice will not demonstrate the full benefit of sapropterin. BH4 responsive women will gain most benefit from sapropterin if it is used during the preconception phase enabling them to cope better with their diet therapy as previously explained.

- Sapropterin also has a role to place post pregnancy. Sapropterin given with a relaxed low phenylalanine diet post pregnancy, may lead to improved maternal mood and ability to cope with parenting leading to better outcome in children. Many women are unable to sustain dietary treatment post pregnancy as they consider a low phenylalanine diet too challenging when caring for their infant. In Waisbren's follow up study of maternal PKU pregnancies, their school aged children were more likely to exhibit learning disabilities, ADHD, or emotional and behavioural disturbances. Their mothers with PKU were more likely to be depressed or anxious. The authors suggested that the environmental circumstances, including the home environment, maternal depression and anxiety contributed to the issues seen. In Waisbren's study although many women perceived themselves as functioning well in their daily life, 25% performed in the borderline intellectual range. *Waisbren SE, Rohr F, Anastasoaie V, Brown M, Harris D, Ozonoff A, Petrides S, Wessel A, Levy HL. Maternal Phenylketonuria: Long-term Outcomes in Offspring and Post-pregnancy Maternal Characteristics. JIMD Rep. 2015;21:23-33.*

Table 5: Child/foetal outcome in maternal PKU

Lead author/ year/ Country	National study/local centre	Number of women	Number of pregnancies	Number of women on treatment pre-conception	Treatment (diet only/diet + kuvan)	Blood Phenylalanine (Phe) control	Infant outcome at birth	Outcome of children at follow up
UK								
Davidson et al (1981)[1] UK	Liverpool (1 centre)	1 woman	1 pregnancy	Diet treatment commenced post-conception.	Only diet	Not available	Asphyxiated without apparent cause and intermittent positive pressure ventilation was necessary. Normal growth.	Normal growth at 5 weeks, 18 weeks and 38 weeks.
Farquhar et al (1987)[2] UK	Edinburgh (1 centre)	1 late diagnosed HPA and borderline IQ/ and 1 early diagnosed with classical PKU	2 pregnancies	**Pregnancy 1:** pre-conception diet	Only diet	Target: Blood phe levels <600 μmol/L	**Pregnancy 1:** Normal weight (10^{th} - 25^{th} centile) and head circumference (25^{th} - 50^{th} centile) **Pregnancy 2:** Normal weight and head circumference (3^{rd} - 10^{th} centile)	**Pregnancy 1:** **Weight at:** **6 months –** 10^{th} – 25^{th} centile; **1y** – 3^{rd} -10^{th} centile; **2y** – 10^{th} – 25^{th} centile; **3y** - 10^{th} – 25^{th} centile **Head circumference at:** **6 months** – 25^{th} centile; **1y** – 25^{th} -50^{th} centile; **2y** – 25^{th} -50^{th} centile; **3y** - 25^{th} -50^{th} centile **Pregnancy 2:** **Weight at:** **6 months** – 50^{th} – 75^{th} centile; **1y** – 10^{th} – 25^{th} centile **Head circumference at:** **6 months** – 25^{th} -50^{th} centile; **1y** – 10^{th} -25^{th} centile
Davidson et al (1989)[3] UK	Liverpool (1 centre)	By 1990 estimated 2000 fertile PKU women in the UK. In that centre: 61 out of 106 patients under follow up were females 16 patients had pregnancies	8 pregnancies (3 therapeutic abortion - 2 medical advice and 1 personal choice) Remaining 5 started either diet or contraception	1 woman on pre-conception diet 7 women diet treatment commenced post-conception diet	Only diet	Mean levels during pregnancy below 0.6 mmol/l	**Diet treatment commenced post-conception:** 1/7 spontaneous abortion and 1/7 hydatidiform hole. **<u>Diet treatment commenced post-conception:</u>** **Patient 1:** Birth asphyxia **Patient 2:** forceps and epicanthic folds **Patient 3:** Normal **Patient 4:** Ventouse extraction, shoulder	**<u>Long-term follow-up of 4 infants:</u>** 1 attended normal school and average progress. 1 started school, reads but has strabismus and epicanthic folds. 1 patient with mild phonological and expressive language problems. Environmental deprivation. 1 patient has asthma

							dystocia and neonatal cerebral irritation. **Patient 5:** Narrow palpebral fissures with creases on ear lobes **<u>Diet treatment commenced pre-conception diet:</u>** **Patient 6:** Normal 1/6 with birth weight below 3rd centile.	
Brenton et al (1996)[4] UK	South East England (1 centre)	Not available	N =**39**	**33** infants from mothers on pre-conception diet (34 births and 22 mothers) **6** infants from mothers on diet treatment post-conception (6 births and 5 mothers)	Only diet	**1st trimester**: 9/32 on pre-conception diet with median levels >300μmol/L **2nd trimester:** 3/32 on preconception diet with median levels >300μmol/L **3rd trimester:** 2/32 on preconception diet with median levels >300μmol/L	**6 pregnancies (commenced diet treatment post-conception):** 2 died of severe congenital heart disease. 1 had coarction of the aorta.	1/27 developmental quotients at age 1y below normal 6/13 general cognitive index at the age of 4y below normal
Magee et al (2002)[5] UK	Northern Ireland (1 centre)	5 women with HPA (IQ in 3: 96, 101 and 104) and 11 Classical PKU (IQ between 73 and 102)	11 pregnancies from HPA and 28 pregnancies from classical PKU **Total: 39 pregnancies**	18 pregnancies on pre-conception diet, 14 pregnancies commenced diet post-conception diet and 7 pregnancies on no dietary treatment.	Only diet	Not available	**<u>HPA:</u>** 1 mild development delay and 1 infant was diagnosed with Classical PKU. **<u>Classical PKU</u>** 1 miscarriage. 2 stillbirth and anencephaly. 9/27 had congenital anomaly with 6/21 have some degree of delay. **Pre-conception diet (n=11):** 1 stillborn and 1 congenital heart defect. **Commenced dietary treatment post-conception in 1st trimester (n=7):** 3 congenital abnormality (anencephaly, unilateral talipes and pyloric stenosis)	**Pre-conception diet (n=11):** 1 child has borderline IQ

							Commenced dietary treatment post-conception in 2nd trimester (n=2): 1 infant with anomalies and severe development delay (deletion of 4p chromosome) 1 infant microcephaly **No dietary treatment (n=5):** 4 mild to moderate mental retardation, 2 microcephalic and 1 had congenital heart defects, gastroschisis and subglottic stenosis.	
Lee et al (2003)[6] UK	One centre (London – Charles Dent)	Not available	79 infants	61 infants on pre-conception diet 18 infants started diet post-conception	Only diet	**Pre-conception diet:** 273 μmol/L (1st trimester); 191 (2nd trimester); 224 (3rd trimester) **Commenced diet Post-conception:** 536 μmol/L (1st trimester); 249 (2nd trimester); 267 (3rd trimester)	1 infant had mild HPA and 1 unrecognized neurodevelopment dysmorphic syndrome. **Started dietary treatment post-conception:** 4 congenital heart disease and 2 of them died. **Pre vs post-conception diet:** Head circumference (34.2 vs. 32.9cm) and weight (3.20 vs. 2.89kg).	**Griffiths development quotient at 1y (Pre- vs post-conception):** 110 vs 106 **McCarthy IQ at 4y (Pre- vs post-conception):** 90 VS 83 **Wechsler Intelligence Scale for children at 8y (Pre- vs post-conception):** 105 vs 82.5
Lee et al (2005)[7] UK	Maternal PKU registry (database)	155 women	228 pregnancies	110 pregnancies on pre-conception diet, 91 pregnancies commenced dietary treatment post-conception and 18 pregnancies never started Phe restricted diet	Only diet	Not available	**Mean birth weight:** 3160g (Started diet pre-conception), 2818g (commenced dietary treatment post-conception) and 2978g (no dietary treatment). **Head circumference (n=197):** 33.3cm (no dietary treatment), 32.7cm (commenced dietary treatment post-conception) and 33.6 cm (on pre-conception diet).	**Mean DQ at 4y (n=50):** 72.3 (no dietary treatment), 96.8 (post-conception diet) and 108.9 (pre-conception diet). **Mean IQ at 8y (n=32):** 39.5 (no dietary treatment), 86.5 (commenced dietary treatment post-conception) and 103.4 (pre-conception diet).

							Congenital heart disease: 12/72 (started dietary treatment post-conception); 2/84 (pre-conception diet); 1/15 (no dietary treatment)**.**	**Pre-conception diet higher DQ or IQ scores (p=0.03).**
Maillot et al (2008)[8] UK	London (1 centre)	67 women	105 infants (37 had 1 pregnancy; 21 had 2 pregnancies; 6 had 3 pregnancies; 2 had 4 pregnancies; 2 twin pregnancies were excluded)	73 pregnancies on pre-conception diet and 32 on post-conception diet: 32 (average start 9.9 weeks). **Preconception diet:** 4/7 (1997 to 1986); 37/43 (1987 to 1996) and 34/55 (1997 to 2005).	Only diet	Blood Phe target 100-250 μmol/L. **Diet commenced pre vs. post-conception:** Mean Phe: 203.5 vs. 269μmol/L **1st trimester:** 248.8 vs 493.6 μmol/L **2nd trimester:** 172.8 vs. 253.1 μmol/L **3rd trimester:** 183.4 vs. 217 μmol/L	**Pre-conception diet (n=74):** 1 had HPA and 1 neurodevelopment dysmorphic syndrome. **Diet commenced post-conception (n=32):** 1 infant had malformations (dextrocardia and solitary lung), 4 congenital heart disorder and 2 of them died. **Weight z-score:** 0.22 (pre-conception diet) n=69 vs. -0.25 (diet commenced post-conception) n=22 **Occipitofrontal circumference z-score:** 0.42 (pre-conception diet) n=68 vs. -0.96 (diet commenced post-conception) n=21	**Griffiths at 1y:** 107 (pre-conception diet) n=73 vs. 99.3 (post-conception diet) n=27 **McCarthy at 4y:** 95.2 (pre-conception diet) n=54 vs. 85.9 (post-conception diet)) n=14 **WISC-III IQ at 8y:** 110.6 (pre-conception diet) n=30 vs. 91.2 (post-conception diet) n=9 **Negative correlation of blood Phe and McCarthy scale at 4y.** Strongest relation between mean Phe and IQ observed in 1st trimester. Proportion of time >250 mol/L during 1st trimester negatively related to IQ at 4y and 8y.
Jovanovic et al (2011)[9] UK	Newcastle (1 centre)	42 women of reproductive age. 16 women conceived.	20 pregnancies **4 early spontaneous abortions and 4 terminations.**	8/20 pregnancies on pre-conception diet.	Only diet	Target: 60-250 μmol/L. All abortion or terminations related to Phe>1000 μmol/L 11/12 achieved levels <300μmol/L and 9 achieved normal outcome.	1/12 had epilepsy, 1/12 congenital cataracts and 1/12 had congenital heart abnormalities and died at 2 weeks.	Not available
Adam et al (2016)[10] UK	Glasgow, Scotland (1 centre)	17 women	20 pregnancies (21 live births)	11/20 pregnancies on pre-conception diet	Only diet	5/20 pregnancies had blood Phe levels <300 μmol/L pre-conception, 8/20	4/17 had congenital anomalies. **List of anomalies:** cardiac abnormality, flattened	Infant weight z-scores higher in planned pregnancies (0.41 vs -1.04 SD) on follow-up.

				9/20 pregnancies on dietary treatment post-conception		around conception and 16/20 by 12 weeks post conception.	philtrum, cleft palate, severe dysmorphic facial feature with small head size, with laryngomalacia, with lower intestinal anomalies and talipes malformations and hemangioma on toes. % of anomalies lower with pre-conception diet (p=0.005). Infant weight z-score higher in planned pregnancies (0.20 vs -0.41 SD). 1 had head circumference <5th percentile.	
Europe								
De Klerk et al (1987)[11] The Netherlands	1 centre	3 PKU patients from the same family	7 pregnancies	1 pregnancy on pre-conception diet 3 pregnancies diet treatment commenced post-conception. 3 pregnancies with no diet treatment	Only diet	Not available	**Case 1** **Pregnancy 1 (no diet treatment):** Microcephaly Pregnancy 2 (diet post-conception): Low birth weight and head circumference <10th centile **Case 2** **1 abortion** **Pregnancy 3:** No treatment **Pregnancy 4:** No treatment **Pregnancy 5** (diet commenced post conception): Head circumference 10th centile **Case 3** **Pregnancy 6 (pre-conception diet):** normal growth at birth.	**Patient 1 at 4y:** Head circumference on the 3rd centile and mentally retarded **Patient 2 at 1y:** Developed serious breath-holding spells with convulsions. **At 2y and 4 months:** Normal psychomotor development. Head circumference (10th centile). Cardiac murmur without proven anatomic abnormality. Convulsions had ceased from 8 months. **Pregnancy 3:** Mentally retarded. Delayed speech and attends special school. Head circumference on the 10thcentile at 7y. **Pregnancy 4:** Normal head circumference (50th centile) at 5y.

							Pregnancy 7 (post-conception diet): normal growth at birth	**Pregnancy 5:** Normal development. At 3y and 4 months – head circumference on the 3rd centile. **Pregnancy 6:** At 1y and 2 months normal growth and development- Head circumference (90th centile). **Pregnancy 7:** Normal growth and development at 8 months. Head circumference 50th centile
Güttler et al (1990)[12] Denmark	Copenhagen (1 centre)	2 women (Untreated PKU)	4 pregnancies	2 pregnancies on pre-conception diet. 2 untreated pregnancies (one before and one after PKU diagnosis)	Only diet	Levels during pregnancy with pre-conception diet: 0.18-0.42mmol/	**Pregnancy 1 (untreated):** microcephaly and 2600g birth weight **Pregnancy 2 (pre-conception diet):** 37 cm head circumference and 3500g birth weight **Pregnancy 3 (untreated):** 28 cm head circumference and 2060g birth weight **Pregnancy 4 (pre-conception diet):** 32 cm head circumference and 2750g birth weight	**Pregnancy 1 (untreated):** at 13y - IQ 50 **Pregnancy 2 (pre-conception diet):** At 9y 11 months - IQ 105 **Pregnancy 3 (untreated):** At 5y and 2 months - IQ 73 **Pregnancy 4 (pre-conception diet):** At 4y - IQ 119
Cipcic-Schmidt et al (1996)[13] Germany and Austria	Maternal PKU national database (multicentre)	2000 women aged 12-45y with PKU in Germany and 275 gave informed consent	43 pregnancies (34 live births, 1 still birth, 7 elective and 1 spontaneous termination)	15 mothers on pre-conception diet (11 PKU and 4 HPA)	Only diet	**Prior to pregnancy:** 11 PKU and 4 HPA with Phe levels <360μmol/L **1-10 weeks:** 8 PKU and 1 HPA with Phe levels <360μmol/L	**Acceptable blood Phe control achieved by 7-8th week of gestation (n=20):** Head circumference and weight were in the normal range (3rd-97th percentile). No child had a heart defect. **Acceptable blood Phe control achieved later in pregnancy:** lower birth weights and smaller head	The same pattern was true for developmental quotient in Bayley test, at the age of 2 years.

						11-20 weeks: 2 PKU with Phe levels <360μmol/L **>21 weeks:** 3 PKU and 3 HPA	sizes. 5 had microcephaly and 1 child had a heart defect (under control by 16th week). Significant negative correlations were found between start of dietary control and growth parameters (weight r = -0.57 and head circumference = -0.56).	
Feillet et al (2004)[14] France	Multicentre (Nancy, Paris, Angers, Marseille, Lille, Brest)	79 women (53 neonatal screening) 53 classical PKU, 14 had atypical PKU, 6 mild HPA and 6 unknown	135 pregnancies (13 spontaneous abortion and 16 therapeutic abortion)	**Preconception diet:** 57/135 (42%)	Only diet	Not available	**Outcome only available in 124 pregnancies.** 29 Embryopathies and 7 heart defects (only in babies with embryopathy). 38% good outcome in typical PKU and 50% to atypical PKU Microcephaly in 18 out of 20 embryopathies.	Not available
Prick et al (2012)[15] The Netherlands	Review of case series and case reports	Systematic review: 84 mothers (181 pregnancies) Clinic unpublished data: 15 pregnancies from 7 patients (6 HPA and 1 classical PKU) **Total: 88 women**	**Total: 196 pregnancies**	30 pregnancies on pre-conception diet and 40 pregnancies commenced diet post- conception **Total treated pregnancies:** 70 (37 classical, 20 mild and 13 HPA). **No dietary treatment:** 126 pregnancies (56 classical, 33 mild and 33 HPA; 4 unknown)	Only diet	Median upper limit 480μmol/L (150-730). **Untreated pregnancies (n=126):** Blood Phe median throughout pregnancy (979 μmol/L) **Treated pregnancies (n= 70): Median blood Phe untreated** 1110μmol/L; **1st trimester** (572μmol/L); **2nd trimester** (310 μmol/L); **3rd trimester** (260 μmol/L)	**<u>Untreated group</u>** 19 neonates were small for gestational age and 48 had microcephaly. 5 had congenital heart disease and 2 died at the age of 3 and 4 months. **<u>Treated group</u>** 2 had intrauterine fetal death. Of the 62 delivered, 2 did not survive. 1 stillbirth and 1 died of sudden infant death syndrome at week 4. 4 were born small for gestational age and 10 had microcephaly. 2 had congenital heart disease.	**<u>Untreated group</u>** 38/81 had intellectual disability at median 8y. Facial dysmorphism described in 14 neonates 7 had other anomalies, seizure or epilepsy. 3 had brachydactyly and clinodactyly, 2 bifid thumbs, esophageal atresia bladder exstrophy, vertebral malformation or renal anomaly in 1 neonate. **<u>Treated group.</u>** 11/42 had intellectual disability at median age 3.5y and 6 neonates had facial dysmorphism. Cerebral palsy, pyloric stenosis seizures,

								pectus excavatum, polydactyly, clinodactyly and non-synostosis occipital plagiocephaly. **Differences were more significant for microcephaly and intellectual disability. Facial dysmorphism was related to first trimester Phe and congenital heart disease doubled related with Phe per trimester.**
Tessier et al (2012)[16] France	Multicentre	86 women (64 classical PKU, 14 mild, 3 HPA AND 5 unknown)	115 pregnancies (91 newborns) 8 elective abortion, 5 therapeutic abortion, 5 spontaneous abortion and 1 intra uterine fetal death.	78/89 on pre-conception diet	Only diet	Good blood Phe levels (120-300 μmol/L) in 65/87 pregnancies.	**Newborns with measurements (n=86):** Birth weight<-2SD (N=15/86); Birth length <-2SD (n=29/72); Microcephaly (n=23/62); intra uterine growth retardation (n=34/75); 12/26 in blood phe levels <300μmol/L. **2 cases of congenital heart disease.** Birth weight, height and head circumference inversely correlated with high blood Phe during pregnancy. Intra uterine growth retardation related to levels >300 and <120 μmol/L.	Not available
Feillet et al (2014)[17] Europe **Sapropterin**	France, Germany, Belgium, The Netherlands (Multicentre)	8 women (4 mild HPA, 3 mild PKU and 1 classical PKU)	8 pregnancies	4 pregnancies with pre-conception diet and 4 pregnancies with post-conception diet. All patients had above target blood Phe levels before pregnancy.	Diet + Kuvan (response 39% to 73%) with doses from 8 to 20 mg/kg/day Started pre-conception in only 3 patients.	**Targets:** Belgium (120-300μmol/L), France (120-300μmol/L), Germany (120-240μmol/L) and The Netherlands (150-300μmol/L). All levels below 600μmol/L in the 1st	1 baby born with PKU. **All non-PKU babies had normal gestational age (mean 39) and displayed normal birth parameters:** weight (z-score 0.85), height (z-score 1.40) and head circumference (z-score 0.97).	**Normal development in 3 patients at 2 months, 18 months and 5 months.**

					Diet + kuvan: 4 pregnancies. Normal diet + kuvan: 4 pregnancies.	trimester and within recommended target by the 2nd trimester. Patient 8 had highly variable levels and was out of range on the 3rd trimester (possibly non-BH4 responsive – classical PKU, mutations associated with non-responsiveness).	**PKU baby showed low birth parameters:** weight (z-score -1.18), height (z-score -0.63) and circumference (z-score -1.15). Patient 8 had Potter syndrome (probably associated with poor control during 1st trimester) and died on first day of life.	
Aldámiz-Echevarría et al (2014)[18] Spain **Sapropterin**	Bilbao (1 centre)	1 PKU patient early diagnosed with moderate PKU (IQ 80).	1 pregnancy	Unplanned pregnancy (no diet).	Diet + kuvan (46% response and treated with 10 mg/kg/day =500mg)	Target: 100-250 μmol/L Levels at 312 μmol/L at 6 weeks maintaining mean Phe levels 135 μmol/L afterwards.	Pregnancy resulted in delivery at 41 weeks with an Apgar socre of 5 at 1 min and 8 at 5 min. Birth weight 2740g (5th percentile), 51 cm (54th percentile) and head circumference 35 cm (38th percentile).	**At 2y:** normal weight and height , physical and neurological development
Pinto et al (2017)[19] Portugal	Porto (One centre)	1 classical PKU (Levels >1200μmol/L from the age of 3y). At 8y, IQ 77 and 68 at 28y with learning difficulties and high anxiety level.	1 pregnancy	Pre-conception diet	Only diet	Target: 120-240μmol/L Median blood Phe with pre-conception diet was 486μmol/L. Median of 258μmol/L during pregnancy. Trimester 1: 351μmol/L Trimester 2: 234μmol/L Trimester 3: 247μmol/L	Gestation: 39.3 weeks. Infant birth weight 2570g (3rd percentile), 47.5cm (10th percentile) and head circumference 31.5 cm (1st percentile). Normal fetal growth with cephalic biometry near the 5th percentile.	**At 12 months:** Weight (15thpercentile) and length (50th percentile). **Griffiths Mental development scale at 13.6 months:** normal IQ (91) but locomotor skills were delayed and unable to crawl. Head circumference on the 15-50th percentile). Bitemporal narrowing persisted but the father also presented this.
Yildiz et al (2019)[20] Turkey **Sapropterin**	Ankara	32 women (18 Classical PKU, 6 mild/ moderate, 5 untreated and 3 mild HPA).	71 pregnancies (only 45 live births)	5 HPA without treatment: **49/66 untreated pregnancies due to non-adherence with dietary treatment** (29	15 pregnancies on a low Phe diet + 2 pregnancies on Kuvan.	Treated patients had median levels between 2.5 and 3.49 mg/dl.	**11 pregnancies (untreated classical):** 100% had microcephaly and 91% had intellectual disability. **6 live births from mild PKU:** 67% had	Not available

		Only 14 diagnosed by newborn screening.		classical PKU; and 12 of them were medically terminated due to likelihood of PKU syndrome) **17 pregnancies treated with dietary treatment** All pre-conception except 1. (15 on a Phe restricted diet + 2 using kuvan).			microcephaly and 51% had intellectual disability. **Live births of HPA:** 22% had microcephaly and 11% intellectual disability. **3 cases of congenital heart disease in untreated classical PKU. Also 1 case of unilateral agenesis, iridial atrophy, lens opacities, developmental dysplasia of the lip and bilateral pes equinovarus in untreated patients.** **<u>TREATED</u>** 13 live births and 2 spontaneous abortions. No cases of congenital heart disease or intellectual disability. 1 infant born with tracheoesophageal fistula which was resolved.	
Caletti et al (2020)[21] Italy	Bologna (One centre)	7 women (5 classical PKU and 2 mHPA)	10 pregnancies	5 unplanned pregnancies (levels usually within control within 2 weeks of initial assessment but sometimes up to 4 weeks)	Only diet	Target: 120-250μmol/L Levels on average <200μmol/L during pregnancy	Birth weight 2.8kg with 2 infants from the same mother affected by mild intra uterine growth retardation. 1 had congenital heart disorder.	Not available
USA								
Lenke et al (1980)[22] USA	Data base (International – multicentre) of unpublished data + review of published data	**Database:** 155 Women **Published:** 88 women **Unpublished:** 67	**Database:** 524 pregnancies (423 live births and 101 spontaneous abortions) **Published:** 315 pregnancies (260 live births and 55	34 pregnancies on diet. **Only 3 did pre-conception diet.**	Only diet	Not available	**Spontaneous abortions**: 24% (blood Phe >20mg/dl), 30% (16-19mg/dl), 0% (11-15mg/dl) and 8% (3-10mg/dl). **Mental retardation:** 92% (blood Phe >20mg/dl), 73% (16-19mg/dl), 22%	**Mean infant's IQ <75:** 91% (blood Phe >20mg/dl), 89% (16-19 mg/dl), 25% (11-15mg/dl) and 33% (3-10mg/dl). **Mean infant's IQ 75-90:** 9% (blood Phe >20mg/dl), 11% (16-19

			spontaneous abortions) **Unpublished:** 209 pregnancies (163 live births and 46 spontaneous abortions)				(11-15mg/dl) and 21% (3-10mg/dl). **Microcephaly:** 73% (blood Phe >20mg/dl), 68% (16-19mg/dl), 35% (11-15mg/dl) and 24% (3-10mg/dl). **Congenital heart disease:** 12% (blood Phe >20mg/dl), 15% (16-19mg/dl), 6% (11-15mg/dl) and 0% (3-10mg/dl). **Birth weight <2500g:** 40% (blood Phe >20mg/dl), 52% (16-19mg/dl), 56% (11-15mg/dl) and 13% (3-10mg/dl). Blood Phe: 1 mg/dl = 60 µmol/L	mg/dl), 25% (11-15mg/dl) and 11% (3-10mg/dl). **Mean infant's IQ >90:** 0% (blood Phe >20mg/dl), 0% (16-19 mg/dl), 50% (11-15mg/dl) and 56% (3-10mg/dl). **<u>34 pregnancies on diet</u>** **Diet before conception (n=3):** mean 90 (IQ), 0/3 microcephaly, 0/3 congenital heart disease and 0/3 with birth weight <2500. **Diet started on the 1st trimester(n=11):** 103 (IQ), 2/10 microcephaly, 4/11 congenital heart disease and 0/9 with birth weight <2500g. **Diet started on the 2nd trimester(n=16):** 84 (IQ), 8/15 microcephaly, 2/16 congenital heart disease and 4/12 with birth weight <2500g. **Diet started on the 3rd trimester(n=16):** 79 (IQ), 2/3 microcephaly, 0/4 congenital heart disease and 0/2 with birth weight <2500g.
Levy et al (1984)[23] USA	Not clear	4 women (3 late diagnosed and 1 early treated)	4 pregnancies	2 pregnancies commenced dietary treatment post-conception and 2 pregnancies had no dietary treatment	Only diet	Not available	**2 infants (commenced dietary treatment post conception and no dietary treatment) with head circumference <5th percentile.**	**No dietary treatment:** 1 patient at 3y head circumference (5th centile) and IQ 90 **Dietary treatment commenced post conception:** 1 patient IQ 94 at 2y

Koch et al (1986)[24] USA	Los Angeles (1 centre)	3 women with PKU (2 late diagnosed)	6 pregnancies	5 pregnancies diet commenced post-conception and 1 diet commenced pre-conception	Only diet	**Case 1 (diet commenced post-conception):** blood Phe levels 600-780 μmol/L **Case 2 (diet commenced post-conception):** average blood Phe levels 492 μmol/L **Case 3 (diet commenced post-conception):** average blood Phe levels 588 μmol/L **Case 4 (diet commenced pre-conception without achieving blood Phe levels):** average blood Phe levels 528 μmol/L **Case 5 (diet commenced post-conception):** average blood Phe levels 552 μmol/L	**Case 1:** Head circumference 31.5cm; 50cm length; 2863g birth weight; anterior fontanelle was small. **Case 2:** head circumference 34cm; length 51 cm; 3062g **Case 3:** 35 weeks; 32cm head circumference; 44cm length; 2551g birth weight. **Case 4:** Twins 35 weeks: Twin A normal growth (29.5cm head circumference, 43cm length and 1729g birth weight) Twin B (1843g birth weight, 43cm length and 29.5cm head circumference). Endocardial cushion defect with mitral valve deformity. **Case 5 (Mother of case 4):** 3298g birth weight, 50cm length and 33cm head circumference. Small atrial septal defect.	**Case 1:** Small head persisted to 4y. **Case 2:** At 30 months; DQ 84 in the Gesell development test. **Case 3:** At 22 months anthropometric measurements <5th percentile. **Case 4:** Twin A had a tracheostomy at 2 months due to tracheal stenosis. Gesell testing at 13 months DQ 98. **Twin B:** Infant died at 5 months. **Case 5:** Persistent poor head control at 7 months.
Rohr et al (1987)[25] USA	Boston (New England – Once centre)	From 300 women identified in new England. Study: 10 women (IQ from 65 to 135).	12 pregnancies **Only 5 completed pregnancies (4 classical and 1 HPA).** 6 pregnancies were electively terminated and 1 spontaneous abortion.	1 pregnancy on dietary treatment pre-conception, 3 pregnancies on dietary treatment post-conception and 1 HPA pregnancy on no diet.	Only diet	Not available	Infant from HPA had pulmonary complications due to prematurity which resolved. 2 patients with post-conception diet had microcephaly.	**At 26 months:** infant from HPA had good development and 145 mental score by Bayley scales. **1 child with microcephaly had poor growth and low development; the other child is mentally retarded at the age of 4y.** **Infant from pregnancy with pre-conception dietary treatment grown better.**

Matalon et al (1999)[26] USA	National Collaborative study for Maternal Phenylketonuria (USA, Canada, Germany)	Not available	414 infants	Not available	Only diet	Not available	**31/414 had congenital heart disease (CHD).** **Blood phe <10mg/dl and protein/day <37.5 by week 8:** 0/6 CHD **Blood phe <10mg/dl and protein/day >37.5 by week 8:** 0/76 CHD **Blood phe >10mg/dl and protein/day <37.5 by week 8:** 11/36 CHD **Blood phe >10mg/dl and protein/day >37.5 by week 8:** 11/132 CHD 1 mg/dl = 60 μmol/L	Not available
Matalon et al (2002)[27] USA	Maternal PKU Collaborative Study	Not available	576 pregnancies (162 fetal losses – 76 spontaneous abortions, 80 elective terminations, 3 ectopic pregnancies and 3 stillborn infants). **414 live births**	249 pregnancies started dietary treatment before 8 weeks	Only diet	Target: 120-360μmol/L	22/249 had congenital heart disorder (all 22 were exposed to >600μmol/L in the first 8 weeks). 31/414 had congenital heart disorder for the total sample. 11/36 with congenital heart disorder had natural protein intake <37.5 g/day. 11/132 with congenital heart disorder had natural protein intake >37.5 g/day.	Not available
Keith et al (2003)[28] USA	Maternal PKU collaborative study	Not available	517 pregnancies (416 children live births, however only data available on 413)	Not available	Only diet	Average blood Phe exposure: mean 494 μmol/L (n=412)	**Birth measurements:** weight 3068g, range 1389-4886 (n=411); length 49cm, range 39–56.5 (n=406); head circumference 32.8cm, range 26-38 (n=403).	**Bailey MDI at 1y (n=283):** 100.1 (49-151) **Bailey PDI at 1y (n=265):** 98.1 (49-138) **Bailey MDI at 2y (n=230):** 97.3 (49-151) **Bailey PDI at 2y (n=208):** 99 (49-146) **McCarthy at 4y (n=276):** 85.2 (45-132) **TOLD CSLQ (language development) at 4y (n=255):** 86.1 (34-144)

								WISC-R verbal IQ at 7y (n=284): 92.1 (40-142) **WISC-R performance IQ at 7y (n=285):** 92.0 (40-133) **Results were influenced by blood Phe levels during pregnancy.**
Waisbren et al (2003)[29] USA	Maternal PKU Collaborative Study	Not available	501 infants were eligible. 8 died and the mothers of 44 declined additional data collection. Among 401 eligible, 366 received at least 1 assessment, and only 228 received evaluation at 7y. Compared to 100 controls (only 91 completed assessment).	39 pregnancies on pre-conception diet.	Only diet	Target: <600μmol/L	Not available	**At 7y:** 18% of children had mental retardation, 18% were borderline and 64% average or above in intellectual abilities. % of borderline intellectual ability of those on diet by week 10 decreased from 24% to 5%. Mothers who attained controlled after week 10 stated kids had problems with externalizing behavior, hyperactivity, aggression and poor impulse control. Maternal age, socioeconomic status and IQ at enrollment were lower in HPA compared with controls. **Full-scale IQ:** **Control,** mean 109 (n=63); **untreated MHP,** mean 106 (n=36), blood Phe levels <600 μmol/L **before pregnancy**, mean 105 (n=39); **blood Phe levels <600μmol/L between >0-10 weeks**, mean 100 (n=46), levels blood Phe <600μmol/L between >10-20 weeks, mean 93 (n=44), **blood Phe levels <600μmol/L**

								between >20 weeks or never, mean 72 (n=70). **<u>TOLD – Test of language development:</u>** **Control**, mean 103 (n=59); **untreated MHP**, mean 96 (n=29), **blood Phe levels <600µmol/L before pregnancy,** mean 94 (n=23); **blood Phe levels <600µmol/L between >0-10 weeks,** mean 92 (n=32), **blood Phe levels <600µmol/L between >10-20 weeks,** mean 85 (n=41), **blood Phe levels <600µmol/L between >20 weeks or never,** mean 74 (n=60). **VMI – Visual motor integration:** **Control**, mean 103 (n=44); **untreated MHP,** mean 97 (n=28), **blood Phe levels <600µmol/L before pregnancy,** mean 99 (n=36); **blood Phe levels <600µmol/L between >0-10 weeks,** mean 99 (n=41), **blood Phe levels <600µmol/L between >10-20 weeks,** mean 92 (n=35), **blood Phe levels <600µmol/L between >20 weeks or never,** mean 77 (n=56). **CBCL- Child behaviour check list (total):** **Control**, mean 48 (n=61); **untreated MHP,** mean 49 (n=35), **blood Phe levels <600µmol/L**

								before pregnancy, mean 51 (n=39); **blood Phe levels <600µmol/L between >0-10 weeks,** mean 52 (n=42), **blood Phe levels <600µmol/L between >10-20 weeks,** mean 54 (n=43), **blood Phe levels <600µmol/L between >20 weeks or never,** mean 61 (n=67).
Rouse et al (2004)[30] USA	Maternal PKU Collaborative Study	526 women in the overall study 382 women became pregnant	413 live births (75 spontaneous abortions, 79 elective abortions, 3 ectopic pregnancies and 3 still births).	19 pregnancies in pre-conception diet.	Diet only	19 treated women and blood Phe levels <360 µmol/L before pregnancy, 24 with blood Phe levels <360 µmol/L between week 0-10 weeks. Blood phe levels <600 µmol/L : 60 (before conception), 80 (week 0-10), 80 (week 10-20), 45 (week 20-30) and 90 (after >30 weeks or never). 53 untreated HPA had levels below 600µmol/L with normal diet.	**Sample of 257 pregnancies** 1 infant developed café au lait spot and had neurofibromatosis I. Others had fused ribs, pectus excufvatum or pectus carinatum. Several males had penile chordee. Other abnormalities like hallucal varus, short toes and fingers, atrophic leg, hemiplegia, hydronephrosis, hepatomegaly and brain anomalies of white matter and Turner syndrome. Abnormalities related to Phe control delay. Abnormalities on palpebral fissure length (72%), epicanthic folds (33%) and ears (57%). 49% had more than 3 dysmorphic features related to Phe control increasing from 19% with control before pregnancy to 62% when control not achieved before week 20. 26 had intrauterine growth retardation (none	**McCarthy scores at 4y:** **Pregnancies without congenital heart disease or microcephaly (n=176):** mean 95 **Pregnancies with congenital heart disease (N=7):** 75 **Pregnancies with microcephaly (n=83):** 77 **Pregnancies with congenital heart disease + microcephaly (n=10):** 60

							with blood Phe control before week 10). 3 from pregnancies with blood Phe control between 10-20 weeks, 2 between 20-30 weeks and 21 after that. 137/413 (8%) had microcephaly. 8% when blood phe control achieved before pregnancy, 18% up to 10 weeks, 45% controlled by week 10-20 and 67% not in blood Phe control by week 30. 32 infants with congenital heart disease in addition to 22 multiple defects and 15 isolated defects. None when blood Phe control achieved before pregnancy, 3 when achieved between week 0-10, 11 between week 10-20 and 18 after week 20. **Postnatal growth restriction in 65/257 infants. 6% in women with blood phe control before conception to 67% without control before week 30.**	
Yano et al (2014)[31] USA	Maternal PKU collaborative study	Not available	416 pregnancies	Not available	Only diet	Not available	**28 newborns with congenital heart disease (CHD). Higher blood phe levels and lower plasma amino acids were present in this group.** **No CHD (n=388) vs CHD (N=28):** Median blood Phe levels 556 vs 12227μmol/L, protein intake 68 vs 39g,	Not available

							Phe intake 543 mg vs 802mg.	
Rest of the world								
Ng et al (2003)[32] Australia	Western Australia (patients followed by one centre. Data collected on the Western Australian Maternal PKU program (WAMPKUP)	9 women	30 pregnancies (1 twin pregnancy) **7 spontaneous abortions and 7 elective terminations. Total: 16 live births**	9 pregnancies on pre-conception diet and 7 pregnancies on post-conception diet	Only diet	Target: 360 µmol/L. The majority did not achieve <600µmol/L until the 3rd trimester. Of 9 cases with follow up, 5 were associated with blood Phe levels <600µmol/L by 13 weeks and 7 cases by 15 weeks. Blood Phe control also related to mother's IQ.	15/16 delivered at term >37 weeks. 1 delivered at 32 weeks (post-conception diet). **Excluding pre-term:** mean birth weight 3028gand head circumference 33.1 cm.	Correlation between lower offspring FSIQ (Full scale IQ) scores and later attainment of metabolic control. **Age of assessment varied from 1.5 to 10 y (n=9)** 2/9 had FSIQ scores below average associated with blood Phe control. 4/9 had presented behavioral problems. 5 pregnancies with metabolic control only achieved after 33 weeks, 4/5 had significant behavioral issues. **Clinically significant behavioural problems (n=4) achieved blood Phe control (mean 35.5 weeks):** FSIQ mean 93 **No clinically significant behavioural problems (n=5) achieved blood Phe control (mean 21.8 weeks):** FSIQ mean 106
Nyuzuki et al (2019)[33] Japan **Sapropterin**	Japan	1 PKU diagnosed by newborn screening (Mild PKU)	1 pregnancy	Preconception diet + Kuvan (From 400mg of Phe to 1000mg with Kuvan)	Diet (1000mg of Phe per day without AA) + Kuvan (10mg/kg = 500mg daily) Dose increased to 20mg/kg at 6 weeks of pregnancy.	Plasma blood Phe were around 500µmol/L before Kuvan treatment. Blood Phe maintained <300µmol/L during pregnancy.	**Healthy infant:** 3498g (1.34 SD) birth weight, 50.1 cm (0.51 SD) lenght and 34cm head circumference (0.53 SD).	**Normal development. Enjoji development scale at 31 months:** 121 (physical movements), 109 (hand movements), 133 basic daily habits, 109 (personal relations), 109 speaking and 121 (understanding language).

								At 43 months: 16kg (0.71 SD) weight, 96 cm (-0.30 SD) height and 49.8 head circumference (-0.05 SD).
Wang et al (2020)[34] China	Beijing (One centre)	172 female patients/ 10 married Total sample: 6 became pregnant	6 pregnancies (1 patient had 2 previous abortions, 1 spontaneous and 1 due to hyperphe)	6 pregnancies on pre-conception diet	Diet only	Blood phe levels between 120-360μmol/L during pregnancy. **<u>Levels within target</u>** **Patient 1:** 75%; **Patient 2:** 67%; **Patient 3:** 35%; **Patient 4:** 87.5%; **Patient 5:** 80.2; **Patient 6:** 48.7%.	Mean gestation period: 38 weeks. Mean birth weight 2888.3g, 49.7cm length and 33.4cm head circumference. **No congenital heart defects or other malformations.** **Low birth weight with patients that had suboptimal control with <70% levels within range:** **Patient 1:** 3050g, 50.2cm and 34cm head circumference **Patient 2:** 2350g, 46.6cm and 31.5 cm head circumference **Patient 3:** 2480g, 48cm and 33 cm head circumference (intrauterine growth retardation) **Patient 4:** 2950g, 48.9cm and 33.3 cm head circumference **Patient 5:** 3300g, 51.5cm and 34.5 head circumference **Patient 6:** 3200g, 53cm and 34 head circumferences	**DQ:** **Patient 1:** 88.2 (normal development) **Patient 2:** 80.6 (at 3y) (Gessel assessment: mild language and fine motor development delays) **Patient 3:** 85.7 (feeding issues in the first 6 months with 6950g with at 1y. Corrected at 19 months with 9000g) **Patient 4:** 98.8 (normal growth) **Patient 5:** 92.5 (normal development) **Patient 6:** 96.2 (normal development: weight 8.9kg, 69.7cm at 7.3 months)
Multicentre								
Drogari et al (1987)[35] UK, Australia, Czechoslovakia, Holland,	Multicentre	UK: 81 pregnancies notified to Medical research Council/department of Health and Social	**<u>UK</u>** 35 were terminated, 5 spontaneous early fetal loss and 1	**<u>Group 1</u>** 17 pregnancies on pre-conception diet with blood phe <601μmol/L	Only diet	**<u>Group 1</u>** Only 9/17 patients and 12/17 in the 2nd semester achieved	**Group 1 (n=17):** Mean weight 3512g and head circumference 35.1 cm Malformations: 0	Not available

Switzerland, Denmark, Italy and Poland		security phenylketonuria register in 1986 Non-UK members invited through the SSIEM in 1986: 29 infants	still birth. 3 patients had incomplete data. Final sample: 37 pregnancies **Non-UK:** Data incomplete in 2 patients. Final sample: 27 pregnancies **Total:** 64 pregnancies from 47 women	**<u>Group 2</u>** 12 pregnancies diet treatment commenced post-conception. **<u>Group 3</u>** 9 pregnancies post-conception diet commenced in 1st trimester. **<u>Group 4</u>** 8 pregnancies started post-conception diet in 2nd or 3rd trimester. **<u>Group 5</u>** 18 pregnancies with no diet		good blood Phe control. **<u>Group 2 and 3</u>** Only 1 in 21 patients achieved good control. In the 2nd semester control improved in 14/21.	**Group 2 (n=12):** Mean weight 3105g and head circumference 33.1 cm Malformations: 1 Hypospadias **Group 3 (n=9):** Mean weight 2882g and head circumference 32.9 cm **Group 4 (n=8):** Mean weight 2875g and head circumference 33.1 cm **Group 3/4 (n=17):** Malformations: 4 Aortic stenosis/ tetralogy of fallot, hypertelorism, Coloborna **Group 5 (n=18):** Mean weight 2843g and head circumference 31.1 cm Malformations: 5 Patent ductus arteriosus, hydrocele, anal fistula, aortic stenosis and malformed eyelid.	
Rouse et al (1997)[36] USA, Canada, Germany	Maternal PKU Colaborative study	Not available	468 pregnancies (only 331 live births) 131 terminations (61 spontaneous and 70 elective); 2 still births and 2 ectopic pregnancies. **Final sample:** 134 classical PKU, 42 atypical PKU and 37 HPA; 14 unknown	**Not treated:** 3 classical, 1 atypical and 35 HPA. **Pre-conception diet:** 12 atypical and 30 classical PKU. **Diet commenced post-conception:** **0-10 weeks:** 19 Atypical PKU and 70 Classical PKU **>10 weeks:** 10 atypical and 31 classical	Only diet	Not available	There were 65 children with one abnormality and 36 with two or more congenital abnormalities. Facial structure was abnormal even at well controlled level in 50% or more of the cohort at 8-12 weeks gestation. **<u>On 188 pregnancies</u>** **Blood Phe levels 120-360 µmol/L:** 6% had microcephaly, 4% had postnatal growth retardation. **Blood Phe levels 361-600 µmol/L:** 15% had microcephaly and 2% intrauterine growth	Not available

							retardation and 22% postnatal growth retardation. **Of 52 pregnancies with good metabolic control, only 2 had neurological abnormalities.** **14% of those with levels between 361 and 600 µmol/L had motor delay, 13% abnormal tone and 11% abnormal reflexes.** **28/204 had congenital heart disease and 6 died.** **All had levels >600µmol/L during the first 8 weeks except 1 that had levels 361-600 µmol/L.**	
Koch et al (2000)[37] USA, Germany, Denmark	Multicenter	382 women	572 pregnancies (360 classical PKU, 86 Atypical PKU and 45 HPA)	147 pregnancies on pre-conception diet	Only diet	15.9% of pregnancies resulting in live births started pre-conception and maintained PHE levels below 600 µmol/L . 18.4% of pregnancies had blood Phe levels within target by week 10. 55 women (hyperphe) were untreated with a Phe restricted diet because their blood Phe levels were within the treatment range.	23% microcephaly **Birth measurements (median):** **Length:** 63rd percentile (HPA); 59th percentile (Pre-conception diet); 47th percentile (diet started at 0-10 weeks); 43rd percentile (diet started 10-20 weeks); 18th percentile (>20 weeks) **Weight:** 42nd percentile (HPA); 37th percentile (Pre-conception diet) 28th percentile (diet started at 0-10 weeks); 36th percentile (diet started at 10-20 weeks) 13th percentile (diet started >20 weeks). **Head circumference:** 28th percentile (HPA); 28th percentile pre-conception diet); 34th percentile (diet started 0-10 weeks); 15th percentile (diet started at	**McCarty cognitive scores at 4 years:** **HPA (n=33):** 99 **Pre-conception (n=17):** 99 **0-10 weeks (n=26):** 88 **10-20 weeks (n=48):** 85 **>20 weeks (n=59):** 72 Also connected with lower mother's IQ.

							10-20 weeks); 4th percentile (diet started >20 weeks) **<u>Congenital heart disease:</u>** caused 6 deaths in pregnancies not controlled by 8 weeks Tracheoesophageal fistula (n=1); esophageal atresia (n=2); Elective terminations (n=79); spontaneous abortions (n=75); still births (n=3) - 1 pre-conception diet and 2 started 1st trimester); ectopic pregnancies (n=3; treatment by 4-8 weeks).	
Koch et al (2003)[38] USA, Germany, Denmark ***Same study as previous one but more outcome results**	Multicentre	382 women	572 pregnancies	Not available	Only diet	**WISC-R at age 6 to 7 years (mean):** **Pre-conception (n=18; <360µmol/L):** 104 **Pre-conception (n=29; 360-600 µmol/L):** 104 **Diet started 0-10 weeks:** **(n=14; <360µmol/L):** 103 **Diet started 0-10 weeks:** **(n=47; 360-600 µmol/L):** 99 **Untreated MHP (N=31; <360µmol/L):** 100	Not available	**At 4y (McCarthy mean IQ):** **Pre-conception diet (n=31):** 99 **Diet started at 0-10 weeks (n=51):** 93 **Diet started at 10-20 weeks (n=59):** 85 **Diet started at 20-30 weeks (n=30):** 76 **Diet started at >30 weeks (n=61):** 67 **At 7y (WISC-R mean IQ):** **Pre-conception diet (n=47):** 105 **Diet started at 0-10 weeks (n=61):** 101 **Diet started at 10-20 weeks (n=53):** 93 **Diet started at 20-30 weeks (n=26):** 85 **Diet started at >30 weeks (n=54):** 68

						Untreated MHP (N=9; 360-600 μmol/L): 107		**At 10y (WISC-R mean IQ):** **Pre-conception diet (n=9):** 102 **Diet started at 0-10 weeks (n=20):** 94 **Diet started at 10-20 weeks (n=20):** 93 **Diet started at 20-30 weeks (n=13):** 77 **Diet started at >30 weeks (n=20):** 64
Platt et al (2000)[39] US, Canada, Germany, Denmark	Maternal PKU Collaborative Study		414 pregnancies 257 classical PKU, 91 Mild PKU and 66 HPA.	129 pregnancies on pre-conception diet, 180 pregnancies diet commenced post-conception (1st trimester), 44 pregnancies diet commenced post-conception (2nd trimester), 4 pregnancies diet commenced post-conception (3rd trimester) and 4 pregnancies with no dietary treatment.	Only diet	61 infants from women with blood phe <600 μmol/L before conception. 64 infants from women that stablished diet by week 10.	**162 fetal losses. 31/414 had congenital heart disease and 6 died.**	**Bayley mean scores at 2y (mental scale):** 109, Untreated mild HPA (N=33); 113, Pre-conception control (n=38); 104, control by week 10 (n=44); 106, control between 10 and week 20 (n=55) and 88, control after week 20 (n=73). **Bayley mean scores at 2y (motor scale):** 105, Untreated mild HPA (N=30); 106, Pre-conceptional control (n=37); 102, control by week 10 (n=43); 101, control between 10 and week 20 (n=51) and 90, control after week 20 (n=66). **McCarthy mean general cognitive index (age 4-5y):** 98, Untreated mild HPA (N=26); 100, Pre-conception control (n=11); 90, control by week 10 (n=15); 80, control between 10 and week 20 (n=39) and 70, control after week 20 (n=45).

								McCarthy mean general cognitive index (age >5y): 100, Untreated mild HPA (n=17); 99 Pre-conception control (n=23); 97, control by week 10 (n=18); 94, control between 10 and week 20 (n=38) and 74, control after week 20 (n=45).

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39. L.D. Platt, R. Koch, W.B. Hanley, H.L. Levy, R. Matalon, B. Rouse, F. Trefz, F. de la Cruz, F. Güttler, C. Azen, E.G. Friedman. The international study of pregnancy outcome in women with maternal phenylketonuria: report of a 12-year study. Am J Obstet Gynecol. 2000 Feb;182(2):326-33.

6. COST EFFECTIVENESS MODEL

The following costs do not appear to have been factored in the cost of model used by NICE:

Health care costs

- Cost of any medications such as anti-depressants, ADHD medications, laxatives with diet treated patients with PKU.
- Cost of medical care of co-morbidities – particularly costs of psychiatric, psychology or counselling costs.
- Increased dietetic and health professional costs associated with extra time necessary for counselling when poor metabolic control occurs in patients with PKU.
- Costs of maternal PKU (costs of obstetric care, foetal scans, anti-vomiting medications, maternal hospital admissions, infant cardiac care).
- Costs of nursing time in late treated patients with PKU in care homes.

Community costs

- Cost of GP visits
- Cost of social services involvement with poor blood phenylalanine.
- Cost of additional education in schools or university.
- Costs of extra educational needs of children of women with poorly controlled maternal PKU

Patient costs

- Loss of earnings through time spent managing the diet.

Society costs

- Loss of work productivity

7. DOSE OF SAPROPTERIN

The dose of sapropterin should be an <u>average</u> of 10 mg/kg as patients may need from 5 to 20 mg/kg. Although a <u>maximum</u> dose of 10 mg/kg will be satisfactory for many, there should be the ability to prescribe to a maximum of 20 mg/kg in the patients who benefit from this.

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Sapropterin for treating phenylketonuria [ID1475]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 18 March 2021 **email:** NICE DOCS

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Insert organisation name**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[None]
Name of commentator person completing form:	[**Dr Hugh Lemonde – paediatric IMD consultant, attended Committee meeting as an invited expert, representing BIMDG. The BIMDG has submitted a separate response [DR Elaine Murphy, Chair] – this is my personal response and not the views of the BIMDG**]

Comment number	**Comments**

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Sapropterin for treating phenylketonuria [ID1475]

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I am concerned the age chosen when patients will have to stop Sapropterin (18yrs) will present a particular challenge for young adults with PKU. If they are to retain good Phenylalanine control in adulthood they will have to return to a much stricter diet when they stop Sapropterin at a time when they have just transitioned/are transitioning to adult services. Transition already represents a particularly challenging period and young adults are at risk of disengaging from clinical services. I would recommend, for patients commenced on Sapropterin, that the age of withdrawal of treatment should be extended (for instance to 25yrs)
2	The introduction of a limit of 10mg/kg will exclude some children who are Sapropterin responsive from treatment – evidence suggests that more patients will respond to doses of 20mg/kg than 10mg/kg [Muntau et al 2019], although the proportion of patients who only respond to 20mg/kg will depend on individual genotype and method of response testing. Thus, the numerical impact of this on under 18yr olds in the UK is unclear.
3	Definitions of sapropterin responsiveness and the methodology for testing sapropterin responsiveness are highly variable. It is important that a robust and practical protocol for testing responsiveness is adopted as part of this guidance – lack of such guidance may result in patients being inappropriately labelled as responsive (thus reducing cost effectiveness) and significant inequity of access.
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Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Dr Robin Lachmann

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I have concerns about the need to stop sapropterin treatment at the age of 18. I can understand the argument that it is most important to obtain strict metabolic control in childhood, as the risk of irreversible damage to the brain and permanent loss of IQ is reduced after the age of 10 and is not present in adults. I also agree that treating adults would not be cost effective as the potential benefits from treatment are much less and the patients weigh much more. However, neither of these considerations would lead to a decision to stop treatment at the age of 18. The primary aim of any treatment for PKU must be to prevent irreversible brain damage, but if the funding decision is primarily based on cost effectiveness, then there would be a weight at which treatment was no longer cost-effective. When children reach that weight (perhaps with the proviso that they are also more than 12 years old to definitely prevent loss of IQ points) sapropterin would be stopped. If the goal is to ensure optimum outcomes by treating young people until neurodevelopment has finished, then you wuld continue beyond 18, perhaps until the age of 25. The decision to recommend stopping sapropterin treatment at the age of 18 seems arbitrary and will coincide with a particularly vulnerable period in these young peoples lives. They will be their final year of secondary education, and in many cases will be preparing for exams which will play a large role in determining their futures. Abrupt withdrawal of sapropterin, with the concomitant need for more severe dietary restriction in order to maintain target phenylalanine levels, at this time would be needlessly distressing and disruptive, and might well end up having a real effect on the subsequent course of their lives. I think more sensitive consideration needs to be given to when and how treatment would be withdrawn
2	I have concerns about the decision not to recommend sapropterin for use in women planning pregnancy and in pregnant women with PKU. Although there may be limited evidence on the use of sapropterin in pregnancy, there is a wealth of evidence concerning the teratogenic effects of phenylalanine and the need for women with PKU to obtain strict metabolic control throughout pregnancy. Given that pregnancy is time limited and that the effects of high phenylalanine levels on the children of mothers with PKU are potentially so severe, there should be no question of the cost-effectiveness of sapropterin in this setting. Women with PKU who are planning pregnancy, and the healthcare professionals looking after them need access to every means possible of maintaining phenylalanine levels within the target range for pregnancy. In my view sapropterin should be available to treat all women with PKU who are sapropterin responsive whilst they are trying to maintain phenylalanine levels in the pregnancy range, both during the preconception period and throughout pregnancy. I do not, however, think that sapropterin should be made available to all females of childbearing age whether or not they are currently pregnant or planning pregnancy. Most of these women would have phenylalanine levels well above the pregnancy range and would still need to make significant modifications to their diets when planning pregnancy, or if they had an unplanned pregnancy. The key factor in ensuring optimal pregnancy outcomes for women with PKU is education about the need to plan pregnancy and the availability of as many interventions as possible to help them maintain target phenylalanine levels when deciding to go on a preconception or pregnancy diet.
3	I have concerns about the lack of clear criteria concerning sapropterin responsiveness and the lack of definition of what constitutes a satisfactory response to treatment. One of the major issues in using sapropterin to treat PKU is that it has different effects in different patients. It is important to precisely define which patients are to be considered responsive to sapropterin. This involves describing the method of testing as well as what constitutes an adequate

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	response in terms of lowering phenylalanine and/or increasing natural protein intake. Sapropterin is used as an adjunct to diet. Dietary treatment on its own can be used to achieve target phenylalanine levels in all patients, although this can be very challenging. Therefore, for different patients the goals of adding sapropterin to dietary treatment are different. For some, the goal will be to reduce phenylalanine levels into the normal range whilst for the majority, the goal will be to allow patients to maintain target phenylalanine levels with less dietary restriction. Because of this it is also very important to define criteria for what constitutes a satisfactory long-term response to sapropterin. Without clearly defined definitions of responsiveness and response, it will be very difficult to translate any NICE recommendations into clinical practice. The final recommendations need to address these issues in detail. This has previously been done by a policy working group convened by NHSE and the committee might find it very useful to look at the NHSE policy proposal which resulted from that work.
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Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	I am a patient expert nominated by the **National Society for Phenylketonuria**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None.**
Name of commentator person completing form:	Sharon Buckley

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1	I strongly disagree with the idea that Sapropterin be used as a treatment option for hyperphenylalaninemia in responders only up until the age of 18, for the following reasons: • The recommendation to stop treatment at the age of 18 is reckless and undermines The European Guidelines for the Treatment of PKU that stipulates the need for treatment for life. • The draft recommendation also neglects the whole adult PKU population that are responsive to Sapropterin. • No justification has been provided by the committee as to why the age of 18 has been selected to cease Sapropterin. Neuroimaging research demonstrates that brain development continues beyond the age of 18. For example, the frontal lobes, home to key components of the neural circuitry underlying “executive functions”, are the last areas of the brain to mature and may not be fully developed until halfway through the third decade of life (Sowell et al 92). Indeed, the draft accepts that, *“adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25.”* • In normal circumstances the transition period to adulthood is a continuous process of rapid developmental change that starts accelerating at age 16, and for most, is completed by age 30. During this period, most individuals take steps to live more independently and depend less on family support. These steps, which involve completing school and training, launching work lives, and developing relationships with others, can greatly influence much of their future adult life. The World Health Organization (2020) recognises

	adolescence as one of the most rapid stages of human development and a phase in which biological maturity precedes psychological maturity, noting that the changes taking place during adolescence can have health consequences over the course of a person's life. Therefore, the idea to withdraw a treatment option that would lead to a serious lifestyle change at the age of 18 could drastically interrupt this important developmental period and is therefore unethical. • No guidance has been provided as to how treatment would be stopped, and how services would provide provision for the re-introduction of the ultra-harsh low protein diet. • The cost of these additional services has not been factored into NICE's cost analysis. Children's clinics are often equipped with kitchens to teach the children to cook PKU recipes and demonstrate new products. Most adult PKU clinics are an add-on to another department and don't have the necessary facilities for dietary therapy training. Neither child or adult services normally have dedicated mental health teams and due to the extra load on the mental burden of transition, therefore would be essential to see a requirement of psychological care being added. • NICE does not appear to have taken into account just how greatly Sapropterin liberates the dietary choices a person with PKU can make. It is not going to be easy for a person to switch from eating 40 grams of natural protein to 10 grams of natural protein overnight. • A person's ability to select food and to make decisions about how much to eat is affected by memory for specific eating episodes (episodic memory). Thus, NICE cannot expect a person that has previously been treated with Sapropterin to select low protein foods with ease and without giving thought to the cognitive processes that underpin food selection. • NICE appears to have a simplistic view or indeed has not regarded how eating behaviours are shaped. A child that has learnt what foods they can eat whilst being treated with Kuvan will not simply be able to unlearn those

food choices. Habitual behaviour related to food choices is guided by information about immediate consequences (such as taste, likeability and familiarity) and it is not sensitive to representations of delayed outcomes, (such as the knowledge that eating 2 biscuits would not fall within the day's protein restriction). Habits (so, for example the routine of living with PKU with Sapropterin treatment) are performed automatically and non-consciously and going against the grain of habit (life without Sapropterin and having to learn new dietary habits) is difficult, requiring sustained effort (executive cognitive control, bearing in mind high phe levels reduces cognitive control) to monitor and abandon existing habits, and to acquire new ones.

- Healthy eating (choosing low protein foods) relies on impulse control; therefore, a person with PKU in order to make the right food choices needs to have the ability to inhibit their impulses. Deficits in 'inhibitory control' are often found in people with treated PKU.
- It appears that NICE's recommendation to terminate treatment at aged 18 is because the ERG cost model did not incorporate the benefit of preventing long-term brain damage after the age of 18. Why this was not factored in does not make sense especially when one reads the discussion of clinical considerations accepts that long term brain damage has the potential to occur after the age of 18. Therefore, NICE's decision is discriminatory as the difference in treatment between age groups has not been properly considered or justified.

Bullinger, M. & Quitmann, J. H. (2014). Quality of life as patient-reported outcomes: Principles of assessment Dialogues in Clinical Neuroscience 16(2):137-45

Higgs, S. (2016). Cognitive processing of food rewards. *Appetite* 104, 10–17. doi:10.1016/j.appet.2015.10.003

Hofmann W, Schmeichel BJ, Baddeley AD. Executive functions and self-regulation. *Trends Cogn Sci.* 2012;16(3):174–180. doi: 10.1016/j.tics.2012.01.006.

	Sowell ER, Thompson PM, Holmes CJ, et al. In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. *Nature Neurosci.* 1999;2:859–61.
2	*"There is no clinical trial or registry evidence to show whether Sapropterin reduces the need for a protein-restricted diet or how it affects quality of life".* This is a contentious statement as presently there is no standardised PKU specific instrument via which the true extent of quality of life can be measured/captured in the UK. • Generic instruments are problematic as they lose specificity for the PKU health condition. Also, one has to remember cross-cultural comparability; different countries and cultures may have tested quality of life in patients with PKU and not found improvements in quality of life after using Sapropterin, but that does not mean that the same results would be found in the UK. • Also the committee needs to consider the challenges in assessing quality of life in patients with PKU. For example, PKU is a dynamic condition, and as such it is dependent upon Phe control and therefore neurocognitive function will be variable. Issues with neurocognitive function will affect a person's self-awareness. Many adult patients with PKU have reduced executive function because of high Phe levels and are therefore not as able to assess their own quality of life or put into words their experience (Waisbren, 2010). • It is challenging to collect information on health-related quality of life in adults with PKU. People with PKU can have cognitive problems, self-reflecting and describing their condition. For example, some patients with low IQ and executive dysfunction/communication skills could be unaware, fail to understand or are unable to articulate why they need alternatives to dietary treatment. Indeed, it has been found that some patients are only able to report improvement in functioning and have insight about their deficits after receiving treatment to control their blood Phe, (Simon, 2008).

	• Another reason why a person wouldn't necessarily talk about having a reduced QOL is because, they may not consider that they do so. For example, my son would not be able to affectively put into words how dramatically his life has been negatively impacted by not having control of PKU. One reason he wouldn't talk about having a reduced QOL is because everything that he does in his daily life is about managing all of what he struggles with, consequently and subsequently he manages me to meet all of his needs. He is happy in not going out, he does not need to go to the shops, he does not need to go to work, because he has me. • There is a lack of research when it comes to PKU and the caregivers lived experienced. The management of PKU places a significant burden on carers; there's the gravity of initial diagnosis and the administering of the diet, and it is acknowledged that patients with PKU can suffer from behavioural, mood, emotional, and social problems, psychiatric disorders, intellectual development delays, and neurological deficits. • There is no break from a Phe restricted diet and Sapropterin would help in finding a break. Leaving a patient with PKU for a length of time is not something that carers routinely do due to worries that the patient will not receive the correct foods or that they would be given a forbidden food or that someone else would not adequately manage the diet (i.e. log, weigh and calculate all foods). Waisbren S, & White DA, (2010) Screening for cognitive and social–emotional problems in individuals with PKU: Tools for use in the metabolic clinic. Molecular Genetics and Metabolism. 99:S96 S99.
3	Statements of brain damage - Long term brain damage in adults - NICE has said: "...adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until

	around age 25." NICE has also said "and there is no risk of long-term brain damage in adults". • Neuroimaging research demonstrates that brain development continues beyond the age of 18. For example, the frontal lobes, home to key components of the neural circuitry underlying “executive functions”, are the last areas of the brain to mature and may not be fully developed until halfway through the third decade of life (Sowell et al 92). Indeed, the draft accepts that, *“adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25.”* • Adulthood may represent an additionally vulnerable time for PKU individuals, as the compensational mechanisms for Phe accumulation may be reduced by the normal brain aging processes. Correspondingly, reports provide evidence that some adult PKU patients may develop intellectual disability and mild parkinsonian signs. • Thomas recruited young adults with PKU (average age 27.5) and older adults without PKU (average age 69.2). In both groups, speed of processing was slow and both groups were impaired in their complex executive function (to a similar level) too. Given that the normal ageing brain declines in the aforementioned areas, Thomas concluded that speed of processing and executive function is at risk of declining even further in adults with PKU as they reach older age (a decline that is more than what is seen in normal ageing). Thus, if adults were able to continue restricting their Phe intake the decline in processing speed and executive function could be mitigated, (L Thomas at the ESPKU conference in 2020), Sapropterin would help this. • Piloto et al (2019) evaluated cerebrospinal fluid (CSF) neurotransmitter levels in adults with PKU and age-matched controls. In PKU patients, CSF Phe concentrations were closely related to plasma levels, which were four

	to six times higher than in in controls. The study demonstrates that serotonin and dopamine metabolites are reduced in adult PKU patients and correlate with specific grey matter atrophy patterns. These findings place a focus on serotonin metabolism in the pathophysiology of PKU and may support a more rigorous Phe control, especially in older patients, to prevent. These findings firmly support the idea of treatment for life to prevent early brain damage through aging. • Some adults have low IQ due to poor phenylalanine control in childhood – therefore neurological damage is permanent. There is much evidence to suggest that the inability to sustain good metabolic control in childhood is associated with a decline in IQ score and executive function and will have a negative influence in adulthood (Jahja et al. 2017; Koch et al. 2002; Waisbren et al. 1980). • Waisbren et al, (2007) found that each increase of 100 µmol/l in lifetime Phe for early-treated PKU patients was associated with a 1.9–4.1 reduction in IQ. • Jaha et al 2017 showed that high blood phenylalanine levels in childhood, affect adult cognitive flexibility, executive motor control, executive function in daily life and adult mental health. • Weglage (2013) also showed that high blood phenylalanine levels in childhood and adolescence were related to poorer IQ, information processing and attention in adulthood. Pérez-Dueñas B, Valls-Solé J, Fernández-Alvarez E, et al. Characterization of tremor in phenylketonuric patients. J Neurol. 2005; 252:1328-1334. https://doi.org/10.1007/s00415-005-0860-6. 8. Pilotto A, Blau N, Leks E, et al. Cerebrospinal fluid biogenic amines depletion and brain atrophy in adult patients with phenylketonuria. J Inherit Metab Dis. 2019;1–9. Velema M, Boot E, Engelen M, Hollak C. Parkinsonism in phenylketonuria: a consequence of dopamine depletion? JIMD Reports. 2015;20:35-8.

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4	This statement needs revision "*Children with PKU frequently experience difficulty with focus, depression or anxiety, disordered eating, digestive problems, headaches, low mood and sadness, feeling tired all the time and being in a heightened emotional state (including aggressiveness, psychosis and paranoia) because of high Phe levels."* Thus it was concluded, *"that there is a need for a treatment that can reduce PKU symptoms and give people with PKU and their carers peace of mind about blood Phe levels".* • The above statement is not limited to children, adults have the same experiences too. Adults with PKU and carers of adults with PKU equally need peace of mind about Phe levels.
5	The description of the condition in paragraph 3.1 is incomplete, ignoring the high prevalence of comorbidities which are described at paragraph 2.2.3 of the ERG report. Many patients also have very distorted relationships with food due to the nature of the PKU diet. Losing weight will have an impact on metabolic control; it causes Phe to increase. In addition to this, the supplements (and perhaps the quantities of fruit) whilst being freely available can cause reflux and gastric problems. • People with PKU live with a range of comorbid conditions; disordered eating is a huge problem faced by many living with PKU. The high prevalence of disordered eating patterns has been accepted in the European Guidelines. Page 29, *"living with a lifelong severe dietary restriction may adversely affect eating attitudes and behaviours and increase susceptibility to the development of eating disturbances".* • Below is just one example of a person trying to manage life with PKU whilst also living with other health challenges.

	Case Study A • After my first pregnancy I had to have a spinal fusion as the doctors found I had 4 stress fractures in my spine, and they thought this was due to a condition called Spondylolisthesis. I gained a lot of weight during my first pregnancy due to the high calories that I needed to take on board to keep my phe levels down. However, in order to have the spinal fusion surgery I was told to lose weight. It is so very hard to lose weight on the PKU diet. I felt so very down; I was in pain with my back; I couldn't walk very far. I didn't have a good quality of life and so I swept the PKU diet to one side to lose weight. I now know that was the worst thing I could have done but I was stuck in between a rock and a hard place. I managed to lose 3 stone without following the PKU diet, but I had frequent headaches and I was irritable (I feel similar at the moment). • I had my spinal fusion and tried to keep the weight off but decided I needed to go back on the pku diet but all the high calories I was pumping into my body due the synthetic protein I was eating wasn't good and I put the weight back on again. I also got a stomach ulcer which wasn't helped with all the acidic protein substitute I needed to drink to help me lower my levels. • I am currently trying to find something that agrees with my stomach. In the meantime, I'm having to deal with an awful short-term memory, headaches and poor concentration. These are all signs that my levels are too high. • Despite the fusion I still have a lot of problems with my back. I really need to lose weight (my BMI is in the obese range) but I feel I can't do that as well as be on the PKU diet as it just isn't possible. I have tried many diets to try and see the weight loss. I know if I lose weight it would help my back, but I also need to be on my PKU diet due to the symptoms I am getting. • My second child starts school in September and due to the problems, he was born with I am having to sort lots of things out for him. I need to have a clear head and not the brain fog I have at the minute.

	• I am feeling constantly tired and could quite happily just stay in bed most days. My anxiety is through the roof and I have requested a telephone consultation with my GP, but I can't get one for another month, yet which isn't helpful. I really want to increase as my anxiety meds whilst I know my levels are very high. Another problem with the current PKU dietary treatment is the difficulty getting the food products from the doctors. I require items such as bread and pasta (items most people have in their weekly or monthly shop as part of their staple diet). But my GP will only do a prescription order of one of everything and the bread slices are so small that one loaf isn't enough for two days and one packet of pasta does not see me through. When I do get a prescription and put it in to the pharmacy, I get told that they are out of stock. I have even spoken with the manufacturers myself who assure me everything is in stock, but I am not getting them at all. • Having something like kuvan would be an absolute game changer and I don't understand why adults are being discriminated against the `diet is for life`. when I was younger when we went to see the pku consultant we were told that we could come of the diet it is now advised that the diet is for life. For my own health I need to return to diet and stay on it but something like kuvan would make this so much better and make our quality of life better.
6	The statement at paragraph 3.5 does not adequately describe that many adult patients are dependent on others to help them manage either their dietary treatment or the impairments they have as a result of PKU. - NICE has not taken into account the effect that PKU has on family members that help manage PKU symptoms or PKU treatments. • Adults that do manage the dietary treatment usually only do so because of the support they receive from parents and or partners.

	• In the patient expert report I submitted, I clearly wrote about the care I provide for my adult children; one needing constant mental health support, whilst the other is in need of support to manage the diet. Many adults are in the same position as my daughter; her ability to adequately manage the PKU diet is compromised as she is not left with enough hours to do all of her prescription orders, shopping and cooking. Not being able to have a full-time job places serious economic disadvantages upon people in the same position as my daughter.
7	*"NICE concludes that it was not possible to recommend KUVAN in any group of adults due to the cost effectiveness estimates in adults".* NICE has failed to consider the great wealth of evidence in relation to maternal PKU and the benefit to children born to a PKU mother. This treatment is not fair or just. Women of childbearing age should be given the treatment of Kuvan for the following reasons: • The rate of unplanned pregnancy for women with PKU is the same as the general population. Women with PKU have the right to have sex and the right to have their reproductive rights supported in a non-discriminatory way. • Many women with PKU are petrified of becoming pregnant (whether planned or not) in case their Phe levels would be damaging to the unborn child, (Ford, O'Driscoll, & MacDonald, 2018, https://pubmed.ncbi.nlm.nih.gov/30416967/). Below is a real and typical example of how women in the UK feel about pregnancy. Case study: B • I have never had a child, however from around age 12, pregnancy has often been a topic of threat. Always discussed with negative connotations, I

	would say I fear falling pregnant. I see pregnancy more as a traumatic event - hopefully avoided versus a happy event that solidifies my purpose as a woman of 'childbearing age'. The language around PKU pregnancy is predominantly around protection of harm, therefore I only ever view this as something to protect myself against. I also do not share the same perception of pregnancy as other young women my age, for them it is a wonderful surprise and an even marked in the calendar. For me, it is a long conversation on the phone, organising of endless doctors' appointments, a sit down with the family and sharing of awful news. It is not something I aspire to do, nor be involved in. It's an experience I am scared to let my body endure. • The challenge of identifying and educating women about dietary restriction before pregnancy is highlighted by a study that found 64% of women at risk for embryopathy were unable to achieve blood phenylalanine control by 8 weeks of gestation. Thus, Sapropterin would help in achieving this control. (Brown AS, Fernhoff PM, Waisbren SE, Frazier DM, Singh R, Rohr F, et al. Barriers to successful dietary control among pregnant women with phenylketonuria. Genet Med 2002;4:84–9). • An American study on maternal PKU was conducted in 2000 to determine the effect of a phenylalanine (Phe)-restricted diet in reducing the morbidity on the foetus. Of 413 offspring, 137 were born with microcephaly. The study concluded that women with phenylketonuria need to be educated regarding diet for life to help improve diet control before conception and throughout pregnancy. However, educating women with PKU about the effects of PKU in pregnancy is not enough. Women need the additional treatment of Sapropterin to help them feel safe and able to plan carry a healthy pregnancy. (Platt LD, et al. 2000. The international study of pregnancy outcome in women with maternal phenylketonuria: report of a 12-year study. American journal of obstetrics and gynecology, 182(2), 326-333).

	• In addition to complications with excessive phenylalanine, there are data to suggest that markedly low maternal phenylalanine levels, especially during the second and third trimesters, may be associated with intrauterine growth restriction. (Teissier R, Nowak E, Assoun M, Mention K, Cano A, Fouilhoux A, et al. Maternal phenylketonuria: low phenylalaninemia might increase the risk of intra uterine growth retardation. AFDPHE (Association Française pour le Dépistage et la Prévention des Handicaps de l'Enfant). J Inherit Metab Dis 2012;35:993–9). The use of Sapropterin would help stabilise levels. • For ladies that cannot maintain target Phe levels in pregnancy, then being able to access Sapropterin is a welcome option. However, the idea that a pregnant lady has to have unacceptable Phe levels before being able to access Sapropterin is unethical and puts an unborn child at risk. • All women of childbearing age should be routinely allowed a trial of Sapropterin, and if found to be responsive to Sapropterin, then it should be part of their pregnancy care plan and ultimately available to them for the rest of their PKU treatment. • It is unknown how long a woman with PKU would take to become pregnant. Women on a pre-conception diet that may have conditions such as PCOS or endometriosis, may take longer to become pregnant. Therefore, some women with PKU have to endure a more protracted length of time on a highly restricted diet. Potentially, some women may not be able to manage such a long course of time and not become mothers. Case study C • I've always struggled with the PKU diet since I was old enough to manage the diet on my own, I'm always surrounded by temptation, hence why I came off the diet at 15. Trying to get back it is a nightmare. I don't have hopes of becoming pregnant either. I potentially have polycystic ovary syndrome (PCOS).

	• Significant alterations in the levels of plasma amino acids such as tyrosine and phenylalanine have been observed in patients with PCOS. Unni, S. N., Lakshman, L. R., Vaidyanathan, K., Subhakumari, K. N., & Menon, N. L. (2015). Alterations in the levels of plasma amino acids in polycystic ovary syndrome--A pilot study. *The Indian journal of medical research*, *142*(5), 549–554. https://doi.org/10.4103/0971-5916.171281)
8	*"The committee concluded that high blood Phe levels in pregnancy can have harmful effects on the unborn child. Early control of Phe levels, ideally before conception, would reduce the risks"*. But then went on to contradict themselves with the statement that there is "*not enough evidence on how Sapropterin might be used to prevent harm to the unborn child in women with PKU who are pregnant and trying to conceive*". To not recommend the use of Sapropterin to all women of childbearing age is reprehensible. • Maternal phenylketonuria (MPKU) is a well-recognized complication of PKU and one of the most potent teratogenic syndromes of pregnancy. • The fetal brain and heart are particularly vulnerable to high maternal concentrations of phenylalanine. The levels of phenylalanine in fetal blood are higher than would be expected based on the maternal blood levels because phenylalanine crosses the placenta by an active transport process. Children born to women who have PAH deficiency on unrestricted diets have a 92% risk of developmental delays, a 73% risk of microcephaly, and a 12% risk of congenital heart defects as well as growth delay and seizures • Control of maternal blood phenylalanine during pregnancy prevents most if not all of these complications.

9	NICE has not included the costs of preventing neurological damage to the children of women with uncontrolled PKU (ERG report, section 5.5) in their costs calculations. Below are two real examples taken from the community. Case study: D • I have been off diet since the age of eleven. I was 20 years old and not on diet when I conceived my first born. I struggled with being on diet and my Phe levels were high throughout pregnancy. I just couldn't control my Phe levels. The sickness of pregnancy and my change of taste put me off my amino acid supplements. Having zero exchanges also made the diet too hard to stick to. Consequently, my baby wasn't growing properly. By 24 weeks pregnant I had to have a pregnancy MRI and a congenital heart disease scan! Thankfully the heart disease scan revealed my baby's heart to be find but the MRI found my baby had microcephaly also known as PKU syndrome. My whole world crumbled around me, because my diet is hard to control and my levels were so high, my first child was going to be born with microcephaly. His head and body were not growing properly so the hospital decided to do an elective c-section 7 weeks early at 33 weeks +4 days. The decision to deliver him early was made to see if he developed better on the outside than inside. • My baby boy was born in the early months of 2016. We knew from the MRI that he would have microcephaly and that he would have learning difficulties, but I was not sure to what extent. Though my son is PKU-free, PKU has harmed him! My son is now 5, he has speech delay, development delay, ADHD, hyper mobility in his hip joints and knee joints and he didn't say his first word until he was 2 and couldn't walk until he was nearly 3. He isn't speaking in sentences and can only say a few words. He also has difficulty pronouncing words properly. All this is due to my not being able to control my diet and struggling so much during pregnancy.

	• I am now 5 weeks pregnant (March 2021). Again, I conceived off diet, but this time since January 2021 I had been trying to get back on diet because I wanted to conceive a child with my husband. I got my levels down from 952 to 182 in 6 days. But at the end of January 2021, I struggled getting my supplements and PKU food from my new doctor's surgery as they didn't know about PKU. I then was left with no choice but to eat protein foods so I could get through to when they prescribed me my PKU supplements and PKU food to do my diet again. I have always struggled with the PKU dietary treatment, when I found out I was pregnant this time round my levels were 1509. I am very, very scared of the past repeating itself. My levels are scaring me, this harsh dietary treatment is scaring me. This diet is the hardest thing I have ever had to do. Kuvan for pregnancy or for adults who struggle with diet would give people like me a wider option and be able to give us a lot more help and calm our minds when we find out we're pregnant off diet or when we struggle with diet. Off diet, I get headaches, I'm tired, I sleep in, I am depressed, emotional, I cannot think straight, I lose focus, cannot concentrate on certain things, find it hard to hold a conversation and many more things. Since finding out I am now pregnant again, off diet I am worried the past will repeat itself if I struggle again to get my levels down. Kuvan could really help someone like me to improve my health and well-being and mental health by sticking to diet and giving me a wider option to a PKU life and helping keep my levels where they should be for a healthy fulfilled life. Case Study E • During both my pregnancies I had morning sickness and whilst I controlled it in my first pregnancy with anti-sickness drugs and filling up on PKU foods and taking lots of calories the second pregnancy was so different. The protein substitute we take is so acidic and it really does not sit very well on your stomach, that mixed with morning sickness and high levels throughout

	made my second pregnancy very hard. During the final semester I was hospitalized as I could not keep food or drink down and ended up with a NG tube and levels out of control. Consequently, my second child has problems of his own and this made me feel like a failure as a parent. Maternal phenylketonuria. Committee on Genetics. Pediatrics 2008;122:445–9. Waisbren SE, et al. 2014. Maternal phenylketonuria: long-term outcomes in offspring and post-pregnancy maternal characteristics. In JIMD Reports, Volume 21 (pp. 23-33).
10	The committee states that adults with high Phe suffer from, "*impaired executive function, reduced autonomy, impaired social maturity, difficulty forming relationships and neuropsychiatric symptoms such as depression, anxiety and inattention*". How then, does the committee recommend that people suffering from the aforementioned problems lower their Phe without the help of Kuvan? • The burden of treatment is felt more greatly when people suffer with co-morbidities such as depression, anxiety and inattention. Some adults cannot deal with the complexity of their special diet and are unable to properly deal with the diet in the long term, consequently their wellbeing is compromised. • High blood phenylalanine levels are related to poorer IQ, information processing and attention in adulthood. Lower IQ lessens the patient's ability to manage a low phenylalanine diet. Low IQ is linked with social disadvantage (low paid job, living in poverty), which in turn lessens the ability to apply the stringent dietary treatment, (Weglage, 2013). • Overall, non-adherent patients report more emotional issues related to PKU (Borghi et al 2020). Patients receiving BH4 report lower practical and

	emotional impacts because of lower burden of care associated with the diet (Bosch et al 2015). *Borghi L, Moreschi C, Toscano A, Comber P, Vegni E. The PKU & ME study: A qualitative exploration, through co-creative sessions, of attitudes and experience of the disease among adults with phenylketonuria in Italy. Mol Genet Metab Rep 2020;23:100585.* *Bosch AM, Burlina A, Cunningham A et al. Assessment of the impact of phenylketonuria and its treatment on quality of life of patients and parents from seven European countries. Orphanet J Rare Dis 2015;10:80.*
11	*."Clinical experts estimated that 10% to 20% of patients struggle to maintain control of blood Phe levels".* This statement grossly underestimates the true figure of people struggling with their Phe level • The NHS England Commissioning Policy states "*Up to 28% of pre-school children do not attain recommended Phe targets; this figure rises to 79% of teenagers and 88% of adults (Enns et al., 2010)."* • Ford et al in 2018 reported the experiences of over 300 adults with PKU, many described their dietary management as complex and impractical and so abandoned treatment, with some withdrawing from medical. *Ford S, O'Driscoll M, MacDonald A. Living with Phenylketonuria: Lessons from the PKU community. Mol Genet Metab Rep. 2018 Oct 18;17:57-63.*

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.

NICE National Institute for Health and Care Excellence

Sapropterin for treating phenylketonuria [ID1475]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 18 March 2021 **email:** NICE DOCS

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Sapropterin for treating phenylketonuria [ID1475]

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	I am nominated by the **National Society for Phenylketonuria**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None.**
Name of commentator person completing form:	Patient expert

Comment number	Comments

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The recommendation that sapropterin should be used until the age of 18 and then stopped is inappropriate and dangerous. The reasons are set out below: • The guidance accepts that there is a risk of permanent harm to the brain in young people after the age of 18. There is no clinical basis for the proposed stopping criteria at aged 18. The draft guidance also accepts there is a risk of neurological problems from high phe, including brain fog, executive functioning deficits, anxiety and depression. • Children that have grown up using sapropterin do not develop the eating behaviours of children with PKU. In the survey NSPKU undertook of children taking sapropterin, parents described children that enjoyed normal foods – fish and chips, shepherd's pie, yogurt, pizzas and ordinary bread. These foods are forbidden to children were taking sapropterin. Young people with PKU are trained from being weaned to deny themselves foods and to learn the routines and thought processes of the PKU diet. This is a drastic modification of ordinary eating behaviours that requires inculcation from an early age by parents and their metabolic dietitian. Families start trying to teach children they have a "special tummy" from being toddlers. This process continues through different stages of childhood and adolescence, as at each stage the child and the family needs to navigate how they live with a diet that is radically different from "normal". Children raised using sapropterin will have had a radically easier diet and childhood but they will also be less equipped at aged 18 to manage a PKU diet. Therefore the draft guidance will lead to young people who start adulthood without the coping skills and eating behaviours required to control their phenylalanine levels by a strict PKU diet. • NSPKU held community online meetings to discuss the draft guidance attended by about 130 people. Families and individuals expressed concern that the draft guidance indicated that Committee did not understand the realities of living with PKU. It was said that the PKU diet is very hard, requiring families to have to encourage children to accept prescribed low phenylalanine foods and deny themselves foods they might want to eat. Making a switch at 18 would be difficult/impossible. A teenager – aged 15, said he wasn't sure if he would start taking sapropterin as stopping would be so hard. He thought the guidance was wrong. Adults with PKU said – often drawing from their own experiences - that young people at 18 were very vulnerable as they are trying to start an independent life, studying or starting work. An adult with PKU who had taken sapropterin on a clinical trial and then stopped as a young woman thought that withdrawing sapropterin at 18 would cause people to have severe mental health problems. Many people or families have confided in me about mental health breakdowns occurring at this age linked to the struggle to manage PKU dietary therapy independently.

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	• The Committee did not perform any enquiry into whether into the risks of withdrawing sapropterin for young people aged 18. There is no evidence that suggests that individuals can reliably return to the PKU diet once they have stopped. In fact there is evidence that returning to the PKU diet is rarely successful. Young people who have been raised on the PKU diet will not be "returning" to a strict PKU diet, they are being asked to commence something they have never before experienced. Evidence from the general population is that eating behaviours are formed in childhood and modification is difficult. There is no evidence for the assumption that young people, at aged 18, will reliably be able to control their phenylalanine levels by diet. • The Committee did not consider the impact of the recommendation that sapropterin be withdrawn aged 18 on service provision. Transition from paediatric to adult clinics typically occurs at 18 or close to this age. Transition services for children with PKU are not robust with some areas lacking fully developed adult services. It is very common for young people to experience a failure to manage their PKU at this life stage with impacts on their mental health and education. At least in theory, transition should be a gradual process whereby the young person learns the skills to manage their own care as an adult at a time which is developmentally appropriate for them as an individual. The withdrawal of sapropterin would involve a young person having therapy withdrawn at a developmentally inappropriate time – and needing significant input to attempt to learn to manage PKU via strict diet therapy for the first time. Those resources do not exist. • I am able to comment on this issue from my own experience. My son commenced sapropterin treatment on a clinical trial aged 5 which led to him to start eating foods which were once considered "dangerous". These dangerous habits include eating bread, which his metabolic consultant told me I should never let him acquire a taste for! I was told when he was young to avoid giving any ordinary bread to him as then he would realise it tastes nicer than PKU bread. In this early training from the hospital I was told it was safer to completely avoid foods which could lead him into trouble later on. When he started taking Kuvan he inevitably started eating foods which I never thought he ever would. He does not remember eating prescription foods and has grown up with eating and social habits which without sapropterin would lead him to have spiralling phenylalanine levels. He is "sensitive" to high phe which affects his mood and functioning. Withdrawing treatment would risk very poor outcomes for him. It is these considerations which led BioMarin to confirm that supplies would continue for him and the other clinical triallists after the trial ended, as recorded in the BMJ https://www.bmj.com/content/365/bmj.l1874 This was a relief, but I am very concerned about the proposed stopping criteria because I can see the risk that lies ahead. • Any consideration of the risks of withdrawing treatment needs to consider the position of young women with PKU who are likely to becoming sexually active at around age 18, when sapropterin therapy will be withdrawn under the proposed

	guidance. If they are unable to manage their phe levels via diet poor outcomes from pregnancy is a risk. The European Guidelines recommend robust transition planning for young women to mitigate this risk; by definition an abrupt withdrawal of sapropterin treatment will increase risk of young women and their children having children affected by Maternal PKU. • NICE's decision to withdraw treatment at aged 18 is based on the ERG cost model which did not include the benefit of preventing long-term brain damage after the age of 18. This is not logical when the discussion of clinical considerations accepts that long term brain damage <u>can</u> occur after the age of 18. There are also other failings in the costs modelling for adults. In conclusion NICE's decision is discriminatory as the difference in treatment between age groups has not been properly considered or justified.
2	The statements on the risks of long term brain damage in adults are inconsistent and lack robust evidence or investigation. "*Clinical experts explained that brain development peaks at around age 12. After this high Phe levels are unlikely to affect IQ. However, adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25. In adults, high Phe concentrations can result in short-term symptoms, which are considered reversible by lowering Phe levels through diet."* Thereafter this statement is inappropriately simplified further to "*there is no risk of irreversible brain damage in adults with PKU*". • This statement is not accepted but it is manifestly illogical that the same guidance goes on to conclude "*there is no risk of irreversible brain damage in adults with PKU*". By definition "adults" includes people aged 18-25. The statement on the brain developing until "around 25" is vague. • The statement about the risk of irreversible brain damage in adults is inaccurate and oversimplifies (to the point of inaccuracy) statements from Technical Engagement. NICE is under a duty to ensure that the appraisal reflects consensus views on PKU treatment and the overall breadth of professional clinical opinion. I am not aware of any published peer reviewed paper that makes a statement to the effect that there is no risk of irreversible brain damage in adults with PKU. • The draft guidance includes a statement from me as patient expert that there are adult patients with "severe symptoms and irreversible brain damage" but this seems to have been dismissed as incorrect. However the literature includes independent descriptions which corroborate this evidence. The European Guidelines state "*Some adults who have not been treated early and continuously have been reported to develop leukoencephalopathy, spastic paraparesis, brisk reflexes, tremor, Parkinsonism, psychiatric symptoms and vision loss*". There is no statement in the literature which states that there is "no risk of irreversible brain damage" in adults – instead there are more tentative statements that <u>some</u> problems can be improved or even reversed.

	• Similarly, NHS England developed a policy proposition through the Sapropterin Working Group which included a broad committee with metabolic consultants and dietitians. This recommended treatment for children and adults, noting the occurrence of florid neurological abnormalities manifesting in adulthood such as spasticity of the legs and visual loss. • The PKU community is concerned by broad statements about the safety of high phenylalanine levels. In our community many adults live with impairments sustained by high phenylalanine levels when their dietary treatment was stopped in childhood – on the recommendation of metabolic consultants - who said their "brain had sealed" or "stopped developing". Where there is such a difficult history of incorrect advice about high phenylalanine levels ceasing to be a danger the patient community would like to see a cautious and evidence based approach. It is patients and their families who bear the risk. The life span of early treated patients with PKU is still not complete. • Knowledge of the development of the brain has developed in the past decades and continues to develop. NICE needs to ensure that its guidance is based on robust evidence and a cautious approach to uncertainty. It is submitted that the broad statement - that there is no evidence that irreversible brain damage can occur after the age of 25 - is unsound and should be withdrawn. • Professor Shawn Christ was asked to comment on the draft NICE guidance by a member of the PKU community. Shawn Christ, Ph.D. is Associate Professor, Dept of Psychological Sciences, MRI Director, Cognitive Neuroscience Systems (CNS) Core Research Facility, University of Missouri-Columbia. Dr Christ responded by email on 18 March 2021, which was copied to me. He stated "*In glancing through the Appraisal Consultation Document and Committee Papers Document, I was alarmed by the repeated assertion within the texts that "There is no risk of irreversible brain damage in adults with PKU." **In my professional opinion, there is insufficient evidence to make this claim**. The literature supports the notion that phe-related brain damage incurred in adults with PKU is more reversible than brain damage incurred in children – but this does not mean that the brain damage in adults is fully reversible. For example, a number of studies (e.g., Cleary et al, 1995 in JPeds; Clocksin et al, 2021 in MGM) have found improved white matter integrity following phe level reduction in adults. Importantly, however, even after improvement, the white matter integrity in the PKU patients in these studies continued to be compromised relatively to healthy non-PKU individuals. There is a fair amount of research from our lab and others suggesting that higher phe levels in adults are associated with increased risk of neurological, cognitive, and psychological problems. The extent to which these effects are reversible is definitely still an open question. In my opinion, the conclusion that they are completely reversible (as implied in the aforementioned documents) is quite premature and not necessarily supported by the PKU literature or our general understanding of how risk factors such as this work.*"

Sapropterin for treating phenylketonuria [ID1475]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 18 March 2021 **email:** NICE DOCS

	• A recent paper provides a review of neurological cases which presented in adulthood (*P. Jaulent, S. Charriere, F. Feillet, C. Douillard, A. Fouilhoux, et al.. Neurological manifestations in adults with phenylketonuria: new cases and review of the literature. Journal of Neurology, 2020, 267 (2), pp.531-542.*). This reviewed 8 new cases of neurological manifestations in adults with PKU with 22 cases reported in literature. These were adults – mostly early diagnosed and treated who presented with debilitating neurological symptoms such as the inability to walk and visual loss. MRI scans showed white matter lesions in the brain. The review showed that reinstituting treatment to lower phenylalanine levels could improve symptoms. However the review does not support the statement that the adults' problems were all reversible. The cases studies generally show partial improvements, some adults still had brain lesions, sight loss, tremor and other neurological symptoms. The damage was improved with treatment but not reversed. • The review also notes the presence of white matter lesions in patients with phe levels above 600, who are presently considered to be asymptomatic. The paper noted that it is suspected that such lesions are involved in early neurodegenerative disease. • In my role as a patient advocate I see adults who develop neurocognitive symptoms in adulthood or whose daily functioning declines. These are problems that manifest in adulthood and shows evidence of progression. In the course of patient advocacy work, I am aware that many patients have MRI scans showing PKU related damage to the brain. • Further, the emphasis on irreversible neurological harms and reversible harms can mask the unfortunate truth; which is that many patients who have problems like forgetfulness and executive functioning problems cannot sustain dietary treatment and hence are unable to "improve" their symptoms. This was stressed in the NHS England policy which noted that "In adults, neurocognitive and executive function deficits leads to inability to sustain dietary treatment, causing chronic poor blood phenylalanine control with negative impacts on mental health, quality of life, and daily functioning." This was a major factor in the reasoning to recommend sapropterin for all ages. • The draft guidance does not reflect the consensus of opinion about the issues experienced by adults with PKU with high phenylalanine levels. Currently, in the UK, a metabolic consultant at University Hospitals Birmingham NHS Foundation Trust is the principal investigator for an investigational gene therapy for adults with PKU. It seems unlikely that it would be ethical to conduct a clinical trial for an investigational gene therapy for adults with PKU unless there was a strongly held clinical view that the adults had significant ongoing unmet need. Similarly, Pegvaliase is a therapy developed and licensed for adults with PKU with high phenylalanine levels, which has been licensed by the EMA and FDA for adults only

	despite the possibility of very severe allergic reactions. By contrast, this draft guidance presents a picture that adults with PKU suffer very little risk from high phenylalanine levels. The email I have received from Professor Christ suggests that the statements in the draft guidance relating to the risk of high phenylalanine levels in adulthood are contentious and not evidence based. It seems likely that NICE has not accurately reflected the range of clinical views about the experiences of adults with PKU, perhaps due to the fact that it only consulted one professional working with adults with PKU . • In summary, the statement in the guidance about the risks of brain damage over the age of 18 are contradictory and unsound. It does not reflect the consensus of opinion on the disease in adults. There is a continuing risk of brain damage in adults with PKU. In addition many patients with symptoms are unable to sustain dietary treatment. • The draft guidance fails to accurately reflect the risks and experiences of adults with PKU. The approach to cost effectiveness is also unsound as it is based on omissions or flawed assumptions. Therefore the conclusion that the treatment is not cost effective in adults is unsound.
3	This statement is inaccurate and should be removed/corrected: *"Clinical experts estimated that 10% to 20% of patients struggle to maintain control of blood Phe levels*". This is not consistent with published research or other recent consensus statements. This statement should be withdrawn. The NHS England Commissioning Policy states "*Up to 28% of pre-school children do not attain recommended Phe targets; this figure rises to 79% of teenagers and 88% of adults (Enns et al., 2010)."*
4	The draft guidance fails to reflect the prevalence of comorbidities linked to PKU, and their impact on patients and health resources are not accounted for in the ERG model. This means that the provisional recommendations are not a sound and suitable basis for guidance. • The description of the condition in paragraph 3.1 is incomplete, ignoring the high prevalence of comorbidities which are described at paragraph 2.2.3 of the ERG report. • From my experience with NSPKU I support the accuracy of the statement at 2.2.3 of the ERG report as I see these problems very frequently. The PKU diet allows sugar, fruit, some vegetables and fat freely. Normal calorie loss diets will be very challenging. Many patients also have very distorted relationships with food due to the nature of the PKU diet. Losing weight will have an impact on metabolic control; it causes phe to increase. In addition to this, the supplements (and perhaps the quantities of fruit) whilst being freely available can cause reflux and gastric problems. I know a patient with gastritis, obesity and diabetes who feels she cannot

	improve management of one of her conditions without impacting one of the others. • In my view, the ERG report and the draft guidance fails to reflect the high incidence of eating disorders within the PKU population. I know many patients who have been diagnosed with anorexia or have other diagnosed eating disorders. The PKU diet requires a very unnatural, vigilant relationship with food. • The co-morbidities are linked to significant impacts on quality of life, health and health resource use. These issues are relevant and should have been included in the QALY calculation for adult patients.
5	The statement that there are "no strict guidelines or target Phe levels used in clinical practice" for women with PKU who are pregnant is not accurate. The NHS England Commissioning Policy adopted the European Guideline target phe levels for all patients (children, 12+/adults and pregnant women". NICE guidance should be careful to accurately reflect clinical practice/opinion. The evidence review for the NHS England policy (performed by NICE) also referred to the European Guidelines target phe levels.
6	The statement that … "*the outcomes for pregnant women with PKU are better in the UK than in other countries such as the US*" is not evidence based and is not an appropriate statement for inclusion in the guidance in any event. • First the statement itself is not appropriate or clear. What does "other countries such as the US" mean? Countries without public health systems? High income countries? It is not clear why this statement might even have relevance as a measure of outcomes in this context. • Second, whilst there is some data showing poor outcomes in different countries, comparisons across different studies and countries are difficult as there is often different time-frames and different outcome measures. The statement does not have an evidence base to support it. • The NHS England Policy https://www.england.nhs.uk/wp-content/uploads/2013/04/e12-p-a.pdf includes detailed audit requirements. NHS England have confirmed (following a Freedom of Information request submitted by me) that no audit data was held or collected by them. There is no evidence that any outcome data was considered by NHS England in relation to the decision to not review the policy since 2013. • NHS England's continued failure to review this 8 year old policy - which is described as "not optimal" by the clinical experts – may be associated with poor outcomes for women and babies which could have been avoided. When was it realised it was not optimal and what is being done about it? In this overall context, it is offensive to

	include a statement which suggests that worse outcomes in other countries is a relevant factor to raise. • In conclusion, this statement lacks a reasonable evidential base, is unclear and lacks a reasonable purpose for inclusion.
7	The description of the treatment pathway at 3.3 fails to address patients who cannot access the current treatment. As the treatment is self-managed and complex, many individuals cannot access any existing treatment. This is a hugely relevant issue explaining which adjunctive/alternative treatments are required.
8	The statement at paragraph 3.4 that "Clinical experts noted that just over 50% of adults with PKU are on a protein restricted diet, while about 30% of adults have stopped their diet and the other 20% have difficulties maintaining it". • This statement lacks precision. First it is not clear that what is being measured are "adults with PKU" or "adults with PKU in clinic" or "early treated adults with PKU who have had contact with a clinic recently". The statement is not wholly consistent with the percentages given in paragraph 3.1 which say 10-20% of patients "struggle with control". • The different categories of patients are not clearly defined and it is not clear what the purpose of the categories are, either for describing patient's experience or for developing recommendations. In practice, for many patients, they may not be on diet because they can't cope with it. There may be a continuum of experience of struggling with maintaining their levels/ successfully maintaining their levels/ stopped trying to maintain their levels as they can't cope. Assigning people's experience to these categories is not so easy in practice and the categories for many people aren't fixed – they might move between them for different reasons. For example a woman with PKU who experienced many severe PKU related symptoms told me she was able to control her levels because she had a new supportive partner who managed her treatment for her. Without the presence of her partner she had such severe executive functioning problems she couldn't cook safely on her own. Would you describe this situation as "having difficulties" with her diet, or just being "on diet"? As her experience is dependent on an unpaid carer, she is at risk of becoming "off diet" if the carer is no longer able or willing to assist her. The Committee should understand that these "categories" don't necessarily help describe unmet needs in adults with PKU. • The evidential basis for this statement is unclear. Only one adult clinician (London based) contributed to Technical Engagement. Patient cohorts may be different across England for various reasons (e.g. higher economic deprivation in some areas) and there was no mechanism within Technical Engagement to look for the impact of this.
9	This statement needs revision "*Children with PKU frequently experience difficulty with focus, depression or anxiety, disordered eating, digestive problems, headaches, low mood*

	and sadness, feeling tired all the time and being in a heightened emotional state (including aggressiveness, psychosis and paranoia) because of high Phe levels." • All these statements are pertinent to adults with PKU and the guidance should be adjusted accordingly.
10	The statement at paragraph 3.5 does not adequately describe that many adult patients are dependent on others to help them manage either their dietary treatment or the impairments they have as a result of PKU. The patient expert reports submitted to NICE included a statement from a carer who described having to support her adult children with PKU; one of the young adults needed support with managing and maintaining her PKU treatment, and her son has mental health problems related to PKU. Other information about dependency on care in early treated PKU is ignored. Further, as should be apparent to the Committee, the adult patient cohort includes many people with high care needs, who have untreated or late diagnosed PKU. The European Guidelines on PKU note that "*untreated patients with severe intellectual disability and challenging behavioural problems have high support needs and some may live in social welfare homes*." This issue is discussed further below. Cognitive problems and learning disabilities are also prevalent amongst early treated people with PKU and this is also associated with care needs. The guidance fails to account for care needs or carer disutility associated with adults in its costs modelling and this is a significant failing.
11	The statement at paragraph 3.5 ignores the existence of people with undiagnosed/late diagnosed PKU with intellectual disability. This is a blind spot of the entire guidance; even the description of the patient population ignores a consideration of patients who are not attending clinics. A large proportion of people with untreated PKU or late treated PKU do not attend clinics. The issues with late treated/untreated PKU are discussed further below.
12	The ACD does not adequately explore issues relating to people with learning disabilities. • First, I think it is helpful for the Committee to understand how learning disabilities might be present in the PKU cohort. These are – people with untreated PKU, people with late treated PKU, and people with early treated PKU who have PKU related cognitive impairments or other learning disorders. All these groups may not be attending metabolic clinics for care. People with learning disabilities are likely to be over-represented amongst lost to follow-up. Therefore the approach of the ACD - which is to look at who is attending clinics - is problematic from the start. • There is no patient registry, but there has been some work on trying to understand

	patient numbers with untreated PKU. The paper *'Adults with untreated phenylketonuria: out of sight, out of mind" Murphy, The British Journal of Psychiatry* (2008) details a survey to trace people with untreated PKU, estimate patient numbers and to understand their symptoms and behaviour. The discussion suggested that (as of 2008) there would be about 2000 people with untreated PKU in the population if their life expectancy was 65. • Jancar estimated a life expectancy of 57 (*Jancar J. Increased life expectancy in people with untreated phenylketonuria. J Intellect Disabil Res 1998; 42: 97–9*) It is likely that patients with untreated PKU suffer the same decreased life expectancy due to inadequate NHS treatment for people with learning disabilities (NHS England Learning Disability Mortality Review (LeDeR) Program (https://www.england.nhs.uk/wp-content/uploads/2019/05/action-from-learning.pdf). It is not clear if PKU related factors also have an impact on life expectancy. It is reasonable to assume that there are significant numbers of patients with untreated PKU still alive who are not seen in metabolic clinics. It is my understanding that some patients with untreated PKU now do receive follow up care in metabolic clinics but this is unlikely to be comprehensive. • I am also informed that there are younger people with untreated/late treated PKU in the UK due to migration from countries without reliable new-born screening programmes at the time of their birth. • Murphy's paper surveyed the characteristics of individuals with untreated PKU who had been traced (n=79) and showed very high care needs for the patients with untreated PKU. The majority needed 24-h support, had behaviours that put their safety at risk and behaviours that put other's physical safety at risk. A significant proportion had epilepsy. • Brown and Guest, "*Economic impact of feeding a phenylalanine restricted diet to adults with previously untreated phenylketonuria" (Journal of Intellectual Disability Research*") details resource use associated with caring for people with untreated PKU. As of 1998, the mean annual cost for caring for an individual with untreated PKU was £83,996. It also noted the improvements in behaviour and quality of life that resulted from introducing a low phenylalanine diet. This reduced the care costs to £63,348. • The study concludes that the low phenylalanine diet leads to costs savings for the NHS in people with untreated PKU. However it does not include the costs associated with administering the PKU diet to people in care settings. The study also does not include any consideration of improvements to the life expectancy, health or quality of life of the individuals themselves. However it is clear that these would be substantial, as the patients were significantly less distressed and symptomatic. The European Guidelines also reports improvements such as improvement of motor function behaviour, less aggression, improved mood and sociability. It is also possible that patients would have better life expectancy.

	• Murphy's paper examined untreated PKU but we should also consider the population of people with late treated PKU, who will have been born between the invention of dietary therapy in the 1950s and new-born screening in 1969. Some patients in that era were diagnosed relatively swiftly through the earlier screening methods used prior to the Guthrie test, but some were diagnosed much later. This age group is also often affected by misguided medical practices from this era which believed that it was safe to withdraw dietary treatment from children. Within this group of late treated patients there can be wide disparities of outcomes, with some people with high support needs and some living independent lives. Many of patients were discharged from metabolic clinics decades ago. • It might be helpful to provide the Committee with examples of patients born in the 1950's and 60's. (1) One patient born in 1958, did not meet developmental milestones as a baby. After many tests and delays she was diagnosed with PKU. She was treated with PKU dietary treatment until she was about 4 years old, when her parents were told "her brain had sealed". She has never lived independently and now requires care. She has help and companionship from her father, who is now elderly, and a team of carers. She has never returned to a low phenylalanine diet. The family has had no contact from metabolic specialists since 1963. (2) Another patient known to NSPKU had PKU diagnosed in the first few months of life and was taken off PKU dietary treatment aged about 10. She now has many health problems and lives independently with a substantial care package and disability benefits. Her health problems became more significant as she aged. Carers visit several times per day. She has returned to a low phenylalanine diet which helps with her symptoms but the diet is administered by carers. (3) A man, born in the late 1960s and diagnosed via the "nappy test". Ceased dietary treatment in late teens. Now has executive functioning problems and short term memory problems that impact everyday activities. He returned to diet with the support of his clinic to improve his symptoms. His partner and mother supports him to maintain dietary treatment, for example by organising his meals and shopping and reminding him to have his supplements. He could not manage this without support as he struggles with organisation. • I am also aware of patients with early treated PKU who have learning disabilities or PKU related cognitive problems. These issues typically have an impact on whether the individual is able to manage the low phenylalanine diet independently. I am aware of people with PKU in the community who have problems like intense anxiety or problems with executive functioning which is a barrier to them being to getting a new referral to a metabolic clinic and turning up to the appointment. I am also aware of patients with PKU who are supported by informal family care. During the pandemic our helpline became aware of patients who significantly declined because this family care was no longer available – indicating that informal family care masks how many patients are reliant on care that would otherwise have to be publicly funded. I know patients awarded Personal Independence Payment benefits which indicates that the Department for Work and Pensions have assessed the individuals as

	needing help with daily living activities due to their disability. • The literature suggests there are barriers to the introduction of a protein restricted diet with patients with care needs. Many patients with untreated or late treated PKU have rigid behaviours and resist change. I am also aware that care arrangements themselves can be a barrier to a strict PKU diet. Hospitals frequently are unable to provide low phenylalanine diets. Care homes or domiciliary care will also have difficulties administering the diet; which are likely to be more problematic than for parental carers – e.g the high numbers of staff who may have responsibility for supervising the diet of an individual, reliance on external caterers, staff turnover, possibly (in some cases) a lack of motivation to handle a difficult task. • The behaviour and preferences of the individuals themselves may also be a barrier to reducing phenylalanine levels via dietary treatment. I am aware (though our helpline work) of an early treated adult patient who lacked mental capacity. She presented with neurological symptoms in adulthood and had high care needs. She expressed the wish to not return to dietary treatment. It was also noted that the in-patient settings under consideration for caring for her did not have the facilities to administer a low phenylalanine diet. In another case, I am aware of a patient who steals food within her care home environment as she is attracted to tasty foods. Our helpline is in contact with the carer of a late diagnosed patient who has very ingrained eating patterns; she has eaten the exactly the same meal for decades. • It is likely that sapropterin would have advantages for responsive individuals with untreated PKU or late treated PKU with care needs. Vernon (2010) records treating a 46 year old man with untreated PKU with severe mental retardation and behavioural problems. On sapropterin his phe levels reduced from 1255 lmol/L on an unrestricted diet to 308 lmol/L. Carers noted significant behaviorial improvements and indicated care needs lessened. The patient was able to have increased social interactions, and for the first time in his life was able to take a holiday with the other residents in his facility. • Vernon notes that there is low compliance with low phenylalanine diets in patients with untreated PKU and concludes that "*Our observation indicates that a trial of sapropterin is worthwhile even in severely affected PKU patients, and can have beneficial improvements on quality of life in this challenging population in whom dietary modifications may not be possible*." • Jaulent's paper of French case studies of adults presenting with severe neurological problems includes case studies of introducing either sapropterin or diet treatment alone to patients, who we can infer have care needs. Patient 1 was late diagnosed who presented with a disabling hand tremor. The patient was treated with sapropterin and diet leading to an improvement of symptoms and brain abnormalities. Patient 3 was early treated but had sub-optimal treatment in childhood and presented aged 37 with various symptoms including a walking disability. She was treated with sapropterin and diet which led to an improvement of neurological symptoms (with some issues

still ongoing). The majority of the case studies state that patients found it hard to control their phenylalanine levels via the strict diet. (*P. Jaulent, S. Charriere, F. Feillet, C. Douillard, A. Fouilhoux, et al.. Neurological manifestations in adults with phenylketonuria: new cases and review of the literature. Journal of Neurology, 2020, 267 (2), pp.531-542.*

- I am not aware of any UK literature on treating adults with PKU with care needs with sapropterin, presumably due to the persistent lack of access to sapropterin treatment in this country.

- It is likely that there will be significant QALY gains in patients with untreated PKU or late treated PKU with care needs who are able to take sapropterin. These calculations should take into account the significant costs of delivering the strict PKU diet in a social care setting. From my own experience, the dietary modifications required to treat a patient taking sapropterin can be relatively modest and suitable food choices are usually available from standard catering choices. For example, my son, who uses sapropterin, is able to eat hot school lunches from the standard choices the school offers. I believe this experience would indicate that the practical barriers to dietary treatment for patients with care needs could be overcome with sapropterin. There will not be the costs associated with training staff, preparing special foods or weighing phenylalanine portions and supervising food intake. The time associated with administering standard dietary treatment is 19 hours per week; I believe this would not be less for learning disabled adults with care needs. In my view, sapropterin would reduce the care costs associated with reducing phe levels for such patients.

- I am also able to report on the experience of a family whose child has autism. It was difficult for him to adhere to the low phenylalanine diet as he didn't understand it. He had very strong preferences for high protein foods and an aversion to his protein supplement. The family were eventually able to access sapropterin via an individual funding arrangement. The drug allowed the child to manage his phenylalanine levels as the dietary modifications he required became much easier to manage. He could eat the foods he really loved without affecting his phe levels. As his levels improved, his behaviour also improved.

- I therefore invite NICE to take into account that patients with learning disabilities, cognitive impairments and care needs form a significant section of the PKU community and that the ACD has failed to address this adequately. These patients may experience significant QALY gains from being able to use sapropterin, which will both improve their own health and reduce their care needs. The Committee should also take into account that many patients with care needs cannot access dietary treatment for the reasons discussed, and therefore the comparator is "no treatment".

	• The Committee should include a valuation of the cost of care delivered by family members which might otherwise have been provided by the NHS or personal social services as suggested by 5.5.13 of the Methods Guide. As I have attempted to explain, patients with learning disabilities or cognitive impairments typically cannot manage dietary treatment by themselves. Many adults rely upon others to help them adhere to dietary treatment or to manage the effects of high phenylalanine (e.g. tremors, forgetfulness). If informal family care is removed social services care is required to fill in the gaps. • Further, NICE needs to be mindful of the need to contextualise evidential gaps for this group of patients with a rare disease. This group has literally been "out of sight, out of mind" to research and the NHS. NICE cannot use an unreasonable approach to its evidential standards to perpetuate inequality for this group.
13	The statement that there is "*not enough evidence on how sapropterin might be used to prevent harm to the unborn child in women with PKU who are pregnant and trying to conceive*" is wrong and is contradicted by statements within the guidance itself. The failure to make a recommendation to support women and their children was wrong. • In my work for the NSPKU I have been shocked by the unmet need in women with PKU and set out below some issues known to me. • A young woman with PKU previously took Kuvan on a clinical trial as a teenager and young adult. She had responded well. Access to the treatment was subsequently withdrawn. Many years later she became pregnant, on a carefully planned pregnancy with support from her metabolic team. She has always struggled with tolerating protein substitutes and in pregnancy this drastically worsened. She had hyperemeisis and amino acid supplements would trigger vomiting. She was hospitalised during her pregnancy to manage this but had dangerous phenylalanine levels. The stress of the situation was "nerve shredding" for the entire family. She was not offered access to sapropterin through the NHS England policy. She has stated her belief that women should be routinely offered sapropterin to help them through pregnancy. • A lady planned a pregnancy with her metabolic team – this process is called "pre-con" by women with PKU and their dietitians. Getting her levels low enough was a huge struggle requiring support from her extended family and was very stressful. She did not conceive. This unsuccessful "pre-con" went on for a long time. She became convinced she would not conceive without fertility treatment and stopped her pre-con diet because it was so hard to maintain. She then conceived, naturally and completely unexpectedly with high phenylalanine levels. • Women with PKU can find the process of "pre-con" incredibly hard. The process of maintaining ultra low levels requires a huge effort. Women have to monitor the blood levels several times a week, requiring contact with their metabolic team. It must create immense pressure to conceive swiftly, but life is not always like this.

	There is a practice – recommended in the European Guidelines – to refer women to a fertility specialist early if they fail to conceive quickly. I am aware this happens in some clinics in the UK but not universally so. However this will not necessarily reduce the stress of the situation. • Many women may become pregnant without properly engaging on pre-con and present for metabolic care as swiftly as possible but the foetus will have been exposed to high phenylalanine levels at a crucial stage of pregnancy. Only half of PKU pregnancies follow the "textbook" plan for managing PKU in pregnancy. • Within the PKU community I am aware of girls and women who have had unplanned pregnancies which are either entirely concealed or the girl or young woman does not come forward for support until later in her pregnancy. NICE should consider the pressures that may surround young women with PKU. Sex and pregnancy may be stressful and they may feel shame and panic. They may also have issues related to their PKU which may make them vulnerable to an unplanned pregnancy which they then feel unable to confront. Women may have irregular periods or be using a contraceptive method where they do not expect to menstruate and are not aware of their pregnancy for some time. There is also evidence that women with a disability are more likely to experience sex against their will, engage in early sex and risky sexual behaviours, and these issues may be relevant here (*Holdsworth, Sexual behaviours amongst young adults with limiting disabilities, BMJ*). • The rate of unplanned pregnancy for women with PKU is the same as the general population. Women with PKU have the right to have sex and the right to have their reproductive rights supported in a non-discriminatory way. • I have spoken to many young women who are extremely emotional about the prospect of becoming pregnant. They are tearful and worried and sometimes express guilt. In the NSPKU survey it was very difficult to read that some women reported (anonymously) that these fears impacted their relationships and ability to have a sexual relationship (*Ford S, O'Driscoll M, MacDonald A. Reproductive experience of women living with phenylketonuria. Mol Genet Metab Rep. 2018 Nov 2*) • In 2017 I interviewed a woman whose experience was featured anonymously in a booklet produced by NSPKU. She was early diagnosed and treated but her dietary treatment went off the rails as a teenager. She says she suffered very badly with depression in her teens and twenties. It was in this period that she conceived two children who have disabilities linked to Maternal PKU. The woman herself had disability linked to years of high levels. • From my experience of talking to women in the community, having generally poor metabolic control is a risk factor for unplanned pregnancy and poor outcomes.

	• Women with PKU who have had pregnancies affected by Maternal PKU are not at fault. This was not an outcome they chose. However there is guilt and emotional pain. Women have told me about losing pregnancies and the huge loss and pain they feel. A woman has described these issues as a "trauma". Women have told me of naming babies they have lost and grieving for them and marking the anniversaries of their loss. • Discussion about having children with disabilities or problems linked to PKU is also very difficult even within the PKU community. It can be difficult to acknowledge or discuss as women can feel guilt or shame. • Women have also told me that the support offered after birth is not enough. Many people with PKU experience symptoms when there is an abrupt change in their phenylalanine levels – for example headaches, tiredness and dizziness. Women with PKU who have had a baby are faced with the exhaustion of caring for their baby, trying to start breastfeeding, hormonal changes and an abrupt spike in their phenylalanine levels (from ultra low in pregnancy to uncontrolled or poorly controlled post-partum). Thereafter many women say they struggle with the work involved with maintaining a low phenylalanine diet and looking after their baby. • From my experience and knowledge I am aware that some women with PKU are vulnerable to struggling to cope once their baby is born. I am aware of women who have been hospitalised with post-natal depression. They may struggle to commence breast feeding and feel they can't cope. I am also aware of many women who had less severe problems, but which still impacted their experience of early motherhood. • The Committee should understand there can be quite severe problems within families affected by Maternal PKU. For example, women with PKU who have care needs related to their PKU or who have children with disabilities related to Maternal PKU. It is also possible for women with PKU to have children with PKU, where both the mother and the child have cognitive impairments or other issues related to PKU. I am aware of intensive social services involvement with some families with complex needs like this. However there a range of experiences within PKU, with children who thrive and have mothers who provide exemplary care. • There is evidence that women with chronic physical conditions are at higher risk perinatal mental illness from conception to one year after giving birth Chronic physical conditions and risk for perinatal mental illness: A population-based retrospective cohort study". *Hilary K. Brown , Andrew S. Wilton, Joel G. Ray, Cindy-Lee Dennis, Astrid Guttmann, Simone N. Vigod.* I am not aware there is a specific study of this issue for PKU but the risk is likely to be higher due to the particular stresses of pregnancy for women with PKU and the struggles that women with PKU report in maintaining dietary therapy.

	• It is well recognised that the pre-conception, pregnancy and early childhood years are crucial to children's health. Within this appraisal there needs to be an approach which is more sensitive to promoting good outcomes for women with PKU and their children and more sensitive to their own lived experiences. • It is my view that women should have access to sapropterin through their reproductive years. This will encourage women to have close ongoing relationships with their metabolic team, where women can be honest and supported to make educated choices about their sexual behaviour and plans to start a family. Maintaining good metabolic control in young women will reduce risk factors for unplanned pregnancy. Easy access to sapropterin prior to conception would make "pre-con" adherence less onerous and in my view would increase the number of women who conceive with controlled levels. I do not believe that this is a contentious view, for example the NHS England policy accepted that sapropterin makes it easier to sustain low levels, thus improving adherence and then outcomes "the diet becomes more manageable, thus improving dietary adherence." • Sapropterin should not be withdrawn immediately at birth; this is an inappropriate policy which fails to give women and children the support they need to make a good start. Women should not be forced to undergo a change of treatment regime at this very sensitive time. Women with a chronic condition like PKU, who are starting a family should be supported so their children can have a good "first 1000 days of life" which will improve their long term outcomes. • No country in the world has a Maternal PKU policy like the one adopted by NHS England. Nobody thinks its "optimal" but nobody has ever taken the step of replacing it with an "optimal" policy. NICE has a duty to women with PKU to resolve this.
14	[redacted]

	[redacted] Additional comment – This case study is not a far outlier; the elements of emotional pain around baby loss, eating disorders and mental health problems as a young adult are all familiar to me from other women's stories known to me and the comments received in our NSPKU survey.
15	The guidance manifestly fails to make a reasonable cost effectiveness analysis which takes into account the issues experienced by women with PKU and their children. This is because the ERG costs model ignores the harms experienced by women with PKU and their children. As the committee have asked for more comments and evidence on this issue I shall address this further:

	• Maternal PKU is a risk for miscarriage (e.g. *Jovanovic, 2011, Outcomes of pregnancy in maternal phenylketonuria (PKU): the north-east experience* – of 20 pregnancies in the PKU clinic, there were four early spontaneous abortions and four terminations of pregnancy. From our work with women we know these experiences can be emotionally devastating. I presume NICE STA is able to accord some QALY value to the loss of a pregnancy and I would invite the Committee to give this consideration. • Maternal PKU is a risk for cardiac problems which can be serious. The Jovanovic study referred to above refers to 1 of the 20 pregnancies resulting in a child being born with severe congenital cardiac abnormalities who died at 2 weeks. Many other studies show high rates of cardiac problems which will require ongoing medical attention. • Other physical problems referred to in the literature would require medical interventions, eg cleft palate, epilepsy, congenital cataracts. • Children affected by Maternal PKU are also at risk of issues such as microcephaly and learning disorders. These issues will have life-long costs, significantly affecting the quality of life of the individuals and their carers. Children can have a combination of problems which can be very disabling. I am aware of children affected by Maternal PKU who are not able to attend mainstream schools and will not live independently. At the milder side of the spectrum of outcomes, children may need significant extra input at school to assist with issues such as behavioural problems or learning difficulties. I would invite the Committee to reflect these issues into their costs modelling. • There is clear and well established evidence that low levels at conception and in early pregnancy improve outcomes which is acknowledged in the draft guidance but not carried through into the costs modelling or recommendations. • I would invite the Committee to include the assumption that improved access to sapropterin for women would improve outcomes within its costs modelling. • The Committee should account for the experience of women as well as their children. Sapropterin would make pre-conception diet less miserable and stressful. It could make controlling levels during pregnancy easier. It could ease women's experience post-partum. These experiences also have a value which should be recognised within the costs modelling.
16	The process of developing this guidance was inadequate and discriminatory, particularly in the way in which is looked at groups of patients with protected characteristics. **I stress this is not a fault of individuals but the limitations of NICE processes.**

NICE National Institute for Health and Care Excellence

Sapropterin for treating phenylketonuria [ID1475]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 18 March 2021 **email:** NICE DOCS

	• The guidance states it welcomes comments and further evidence about the subgroup affected by Maternal PKU. Many women have been upset and angry by the draft guidance. A female participant in our community meeting for adults to discuss the draft guidance referred to trauma associated with her experience of Maternal PKU. Many women were clearly very upset by it. Some women will have participated in the consultation process and we hope the Committee considers their evidence carefully. However I am also aware that many women find addressing these issues extremely upsetting and writing this down for NICE, within a context that many feel lacks any attempt at empathy – is a form of emotional labour which is too much. In my view it is likely that many women with important evidence to provide will not have participated. Some women have participated but found the whole process very distressing. • There should have been a more careful and sensitive enquiry about the issue of Maternal PKU within the process before this draft guidance was produced. The Committee meeting did not adequately discuss all the issues. This appraisal is multi-faceted, with PKU affecting different groups within the patient cohort in different ways, but the Committee meeting was faced with a fixed time slot which had to deal with all the issues within the allotted time. The Committee meeting itself was very well conducted within the constraints of the process and time allotted, but this left issues which were not properly examined. This process leaves some issues – particularly those affecting groups protected by the Equality Act – particularly disadvantaged. • Technical Engagement included only one consultant working with adults with PKU. It should have included other experts working with adults – for example a metabolic dietitian working with pregnant women with PKU. The metabolic dietitians working with adults– who are often female – typically work very closely with women with PKU in their pregnancies and often have a very good understanding of the lives of their patients. A wider (and less entirely male!) group of clinicians working with adult contributing to Technical Engagement would have helped bring a perspective which is closer to the reality of women's experiences. • The draft guidance refers to inadequacies in the Company's model as they relate to women with PKU and their children. The approach in the Company's model is obviously inappropriate and wrong - for example why are the reproductive years limited to 18-40 when this is not obviously not how women's bodies work? However at least the Company's model made an attempt to account for women's experience. The ERG model ignores the issue completely which makes their guidance manifestly unsound. NICE is the statutory body entrusted with the duty of developing accurate guidance on this issue. If the Company's model is not appropriate NICE is required to conduct its own enquiries to make reasonable evidence based guidance. This has not happened so far.

	• The issues relating to adults with learning disabilities and cognitive impairments have not been adequately explored and this appears to have been due to the same problems with the process. The issue is "hiding in plain sight" when this guidance relates to a condition which causes brain damage. By definition, this cohort includes many adult patients with learning disabilities to various degrees but the issue is dealt with in passing. The consultation process made no attempt to be accessible to patients with learning difficulties or their carers who are often older people who do not use social media or computers.
17	The guidance appears to recommend capping the dose at 10 mg/kg which is not appropriate. The discussion at 3.21 is about <u>average</u> doses which would be used in clinical practice, ie a range of doses, some below 10 mg/kg and some above 10 mg/kg in light of the license for the drug which allows doses from 5 mg/kg to 20 mg/kg. There is no logical basis for capping the dose at 10 mg/kg, rather than simply adopting an average dose across the patient group within the costs modelling. This was the approach adopted by NHS England. I am aware of patients who have had good clinical responses on low doses of sapropterin. These have been in patients funding the treatment privately where there is a significant need to be very careful about using the lowest possible dose. There is also an Irish paper which shows that some patients can be appropriately stabilised on lower doses of sapropterin (Doyle S, O'Regan M, Stenson C, Bracken J, Hendroff U, Agasarova A, Deverell D, Treacy EP. Extended Experience of Lower Dose Sapropterin in Irish Adults with Mild Phenylketonuria, JIMD Rep. 2018;40:71-76.) However some BH4 responsive patients will need higher doses – perhaps particularly if they have less mild PKU. These patients should not be excluded and may have significant benefits from the treatment. The guidance should allow clinicians the freedom to treat patients appropriately within the license. UK clinicians in the NHS will prescribe economically and appropriately. There is no basis for the distinction in the guidance between the average doses adopted for adults or children. It has not been rationalised.
18	The ERG model is not adequate. It does not capture many aspects of the benefits of the technology and this makes the guidance unsound: • At 2.2.3 of the ERG report is a statement that people with PKU have higher rates of physical co-morbidities and are at higher risk of chronic disease. The ERG model did not include this. • The Committee did not include an assumption about health care costs related to treating the issues listed in 2.2.3 of the ERG report. If it is included, to what extent?

	• The NICE reference case states "all direct health effects, whether for patients, or when relevant, carers" should be considered. Carer disutility was not included in the cost effectiveness calculations for adults or for children. Why? • The cost calculation did not include a valuation of the cost of care delivered by family members which might otherwise have been provided by the NHS or personal social services as suggested by 5.5.13 of the Process Guide. Many adults rely upon others to help them adhere to dietary treatment or to manage the effects of high phenylalanine (e.g. tremors, forgetfulness). If informal family care was removed, the costs of supporting these individuals via standard dietary treatment would be substantial. • The draft guidance makes contradictory, unclear and evidentially unsound assumptions about long-term brain damage. NICE did not even include a risk of long-term brain damage in adults to "around 25" within its costs modelling for the over 18s. • The ERG model does not include the cumulative risks associated with high phenylalanine or a poor diet. This is not a logical approach to take when the ERG report states that high blood phe concentrations are linked to an increased risk of chronic diseases. There is also clear evidence about the cumulative harm caused by exposure to high phenylalanine levels. • Healthcare costs for treating PKU and the problems associated with PKU appear to have been underestimated or left out entirely. • The ERG report notes that impaired functioning can impair the ability to reduce phenylalanine levels through diet (2.2.1). Did the cost calculation for adults include an assumption that some adults patients with symptoms cannot "reverse" them and that they are therefore permanent? • NICE has recognised that early control of phe levels - before conception - would reduce the risks to unborn children (3.2). It is noted by NICE that there is a policy allowing for pregnant women with PKU to access sapropterin but that it is "suboptimal" due to the delays in access in early pregnancy being harmful. The decision to ignore the harms suffered by women and their children is therefore not logical. • The Committee has not appropriately contextualised its approach to uncertainty in the evidence. This appraisal concerns a sub-set of a rare disease (BH4 responsive PKU). Within this appraisal are other issues concerning even smaller sub-sets of patients –

	pregnant/maternal women with PKU, or patients with PKU who have significant care needs. These areas are inherently hard to study or will not ever be a target for significant research. NICE methods guide states that in areas of uncertainty in costs modelling "the Committee is aware that the evidence base will necessarily be weaker for some technologies, such as technologies used to treat patients with very rare diseases". The issues in this appraisal are at the far parameters of low prevalence/lower research base of NICE STA. If NICE is to adopt an expectation for gilt-edged evidence for these issues it will inevitably lead to recommendations which are unsound. I would invite the Committee to attempt to overcome these obstacles using feedback from the consultation and other available evidence.
19	The Committee has not adequately addressed its obligation under the Equality Act. There are significant failings in the guidance. In particular • The decision making around women with PKU and their children does not adequately consider their needs. The decision to not make recommendations in relation to this group is not logical in light of the evidence or adequately explained. Both women with PKU, and their disabled children, are protected groups under the Equality Act. • The decision to recommend withdrawing treatment at the age of 18, and not recommending the treatment for adults over the age of 18, discriminates between groups by reason of age. The clinical reasoning for the decision is manifestly inadequate and the costs modelling relied upon by NICE is unsound. • The decision making in the ACD reveals a "blind spot" around adults with PKU with significant care needs. It acknowledges the existence of adults with brain damage and cognitive issues and yet consideration of their situation is lacking. The costs modelling does not account for this group adequately. These learning disabled adults are a protected group under the Equality Act and the process of developing the guidance and making recommendations was not adequate in relation to this group. • The paragraph on "Equalities" at 2.25 does not meet the requirements of the Equality Act or address health inequalities. It lists various protected groups and simply states that it could not identify any group of adults for whom a positive recommendation could be justified given the cost effectiveness estimates in adults. This statement is inadequate as it does not address whether the cost effectiveness estimates are relevant to the groups in question. The decision making does not meet the standards required of the public sector equality duty.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Appraisal consultation web comments **ID1475 sapropterin for phenylketonuria**

No.	Chapter Name	Section	Selected Text	Comment	Question Text	Answer Text	Represents An Org.	Organisation
1				It is very disappointing to read that kuvan has finally been awarded to pku sufferers with such damaging restrictions. These patients have been waiting a very long time for this life changing drug and to be told they are finally being granted it but at half the dose and will be taken away when they reach 18 is heartbreaking. I have a very close friend whose little boy was born with this condition, to say life has been difficult for them over the last almost 7 years is an understatement. The impact of PKU reaches everyone in his life. It is very challenging to throw birthday parties and play dates for fear of giving food to him that he can't have. And then he has to be watched closely to gage how much of that food he has eaten and what is left. This drug at the right dosage could potentially give him a free diet and an unrestricted and normal life. Please please don't then take that away from him when he reaches adulthood, it would be cruel to do so.			No	
2				The metabolic dietetic team at Alder Hey Children's Hospital welcome the draft publication of the NICE guidelines for the use of Sapropterin in PKU and the opportunity to comment on the guidelines. We are pleased to see that we may be able to offer Sapropterin to our PKU patients who are responders in the near future. We have been extremely concerned that this medication has been available for many years now and is widely used across Europe and the world but not in the UK, to the great disappointment of families and professionals across the country. Any treatment which can reduce the burden of the highly restrictive diet that these patients have to endure every day and which impacts on all aspects of their life can only be welcomed. It is therefore very concerning that the guidelines do not recommend the use of this medication beyond the age of 18 years given that the evidence and guidance for the management of PKU should continue lifelong and that brain development is known to continue into early adulthood. Having worked with PKU patients and families for many years including adults, teenagers and managing maternal PKU, it would be unimaginable to remove one treatment and attempt to try to implement a more restrictive diet at a time when everything is changing in their lives. Young people face plenty of challenges when preparing for adult life but for those with chronic health needs, there are many more hurdles. Not only are we transitioning and transferring them to new medical services between the ages 16-18, these young people are considering their future and becoming more independent. We know from experience and research that this is often the period when young people with chronic conditions disengage from medical services and in the case of PKU, relax their diet and put themselves at risk of severe nutritional deficiencies and the effects of raised phenylalanine levels thereby potentially impacting on their health and life outcomes. This is acknowledged in the recommendations for the CQC report on transition: From the pond into the sea – children transition to adult health services. Care Quality Commission (CQC), June 2014: • Commissioners must listen to and learn from young people and their families. • Adolescence/young adulthood should be recognised across the health service as an important developmental phase – with NHS England and Health Education England taking a leadership role. We have sadly had many examples within our service of young people doing very well in school whilst the phenylalanine have been controlled with the support of their family but who do unexpectedly badly at university/college or even drop out of their chosen course. We believe that this is due to them either stopping their diet or struggling to achieve good biochemical control due to the practical difficulties sticking to such a highly restrictive diet. This has also been true for patients struggling in work and in personal relationships. Removing this medical treatment at such a crucial age would potentially significantly reduce their life chances and opportunities. It is also likely to lead to additional demands on health care to support them in either returning to diet to improve biochemical control, mental health support to manage the potential impact on mental health of raised phenylalanine levels and more concentrated support for women with PKU who would like to have a baby and need to keep phenylalanine levels extremely well controlled to protect the fetus. It is our experience that women with PKU who also have children with PKU, struggle to manage their child's diet if they themselves had poor control during their early years or have come off diet in adulthood and are suffering with the effects of raised phenylalanine levels. Both the child and the parent are therefore disadvantaged by their condition and by the limitations placed on treatment options. The introduction of restricted diets at any age is particularly challenging and requires significant support and input from health professionals. We experience this regularly with late diagnosed metabolic conditions such as gyrate atrophy and homocystinuria. These patients require a			No	

				disproportionate amount of support compared with patients who have been treated since birth. In many cases, they do not achieve good biochemical control and therefore have reduced health outcomes. The demand on health care resources is much greater in these patients generally for this reason. We sincerely hope that the committee will reconsider the proposed age restrictions for the use of Saproterin in the UK and allow us to use this drug in our patients life-long if they choose to do so.				
3					Has all of the relevant evidence been taken into account?	Yes	No	
4					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	Not in a position to comment on this	No	
5					Are the recommendations sound and a suitable basis for guidance to the NHS?	No	No	
6					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	Yes age and sex. This decision directly discriminates against certain people	No	

7				The drug should be accessible for people of all ages. If clinical experts say that brain development continues until the age of 25, should Kuvan not be available until at least that age? Capping the dose at 10mg, may mean that some sufferers are unable to benefit from Kuvan at all. PKU not only affects the sufferer, it also has a profound effect on family members and carers. For example, the mother who has so many other responsibilities but then is sick with worry at what their child may be eating at nursery or school. Anxiety surrounding phe levels causes a deterioration in mental health and quality of life for many.			No	
8				This is a fantastic step in the right direction. Reading that the cost of each 30 pill pack of tablets would cost under £600 and represent cost savings of around £10,326 to £15,973 seems to be an under projection. Factoring in every single prescription, the production and delivery of supplements, dietician calls and appointments, the delivery and processing of blood testing kits and samples would be a hefty value. This would be without adding in the value of time for each meeting with a teacher, care provider, guardian or additional time with psychologists and other support networks or the added economical benefit of parents and carers being able to return to work. The age restriction of 18 due to a perceived lower impact of PKU on over 18s or a more costly application of the drug for adults appears short sighted in its lack of interest in the benefits to quality of life for an adult with PKU. Adults with PKU regularly comment on the difficulties of managing work or studies due to the logistics of their condition or the physical, mental and emotional toll. Whilst the risk of permanent and irreversible brain damage may be lessened, the improvement in quality of life for an adult in emotional, physical, social, cultural and mental capacities is no less than that of a child, and I would hope that future progressions and reviews of this recommendation would take that into further consideration. This would be a very positive step in the right direction, and we will be contacting our dietician as soon as possible should the recommendation be finalised.			No	
9					Has all of the relevant evidence been taken into account?	The treatment recommendations for PKU is a protein restricted diet for life. If this is the case then no treatment should stop at 18 years as is recommended in these guidelines. Their is evidence to suggest that the brain is still developing until at least 25 years and beyond. An undetermined, but relatively high , percentage of early and continuously treated patients with PKU have IQ score lower than expected which affects their ability to carry out the diet.	No	
10					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	The cost model I believe is not a reasonable interpretation of the evidence. Many of the physical and health costs are not being considered. Adults who are unable to keep to this strict diet have poor concentration, low mood, depression, anxiety and low motivation . This can result in social and family issues and the ability to work which is costly to society. Many of patients with PKU require counselling and psychology support, a better treatment alternative to diet will decrease these costs. Many families are awarded disability living allowance (DLA) as parents are unable to work fulltime in order to carry out the dietary treatment for their child/children.	No	

11					Are the recommendations sound and a suitable basis for guidance to the NHS?	NICE has said the committee was not aware of any evidence to estimate the benefit of sapropterin to the unborn child of enhanced Phenylalanine level control. In my experience many woman cannot achieve the level of control recommended pre-conception with diet. The help of BH4 to responsive woman wpuld be a help for woman to cope with the diet and sustain the required phe levels during pregnancy. After infants are born, the medication BH4 would help mothers to have better mood/decrease depression and help them to care for their infant..	No	
12					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	Many of patients with PKU live with disadvantage. In my clinical experience working as a metabolic dietitian a number of families have children with learning difficulties due to poorly controlled Phenylalanine levels. These children are disadvantaged as they are unable to adhere to this very difficult diet. As they grow up into teenagers and young adults this continues as they will not be able to achieve a high level of education and obtain well paid jobs that they would have had if they had not PKU. To recommend to stop treatment at 18 would be to disadvanatage young people with PKU. At this age as they transition to live away from home, start jobs, go to university they would have to learn a new diet treatment which would likely result in poor phe control and lead to issues with low mood, poor concentration.	No	
13					Has all of the relevant evidence been taken into account?	I do not think that all the evidence has been taken into account. As a Clinical Psychologist working in an Adult Inherited Metabolic Disorders (IMD) clinic, I have referrals for anxiety and mood associated with having difficulties staying on diet to support PKU . This is a rare condition and there are in fact only 3 Adult Clinical Psychologists working in this field clinically in England. The largest patient group referred to the IMD Clinical psychologist is PKU and typically makes up almost a quarter of all referrals. The referrals typically relate to quality of life issues, diet adherence and anxiety, stress and low mood and reflects the complex biopsychosocial factors involved with this condition. But in particular all the referrals relate to diet and managing the treatment which seems to present a burden to a lot of patients adding to their stress, mood and anxiety. In terms of evidence, clinically I want to add that I have noticed that the stress of diet and supplements seems to place a considerable strain in itself on patients and impacts on their mental health and quality of life. I have only had 2 referrals for patients with anxiety and low mood associated with having PKU who were also taking Kuvan . Over time I have noticed that clinically they have reported significant improvements to their quality of life, mood and anxiety. In particular one patient, a 31 year old woman, I was offering a CBT based approach , had therapy in the past but since taking Kuvan, said she had noticed that she has unhelpful thoughts but is able to keep them in check now and stops things from escalating. She said noticing her levels at 300 with 6 exchanges is “phenomenal”. She is able to enjoy 6 exchanges as opposed to 3. She appreciates that she has a more severe case of PKU and said that despite the small improvement to exchanges, she feels she is better able to manage her therapy and anxiety now because her mind is less full of issues to do with food and levels. Kuvan she said has helped her to concentrate “massively”. She said to me “Kuvan is not about coming off diet but is so much more than	Yes	Inherited Metabolic Team , QEH, NHS

						that". I wondered with her about functioning and quality of life. We both felt that her ability to concentrate as a result of not having to think all the time about levels and diet has improved her quality of life and enabled her to manage a life with PKU that still involves diet, but has enhanced her life so that she is better able to manage it and its associated treatments. Her anxiety has greatly improved and her panic attacks have reduced significantly as a result. We have wondered together in our sessions, if she had had the Kuvan from 18 rather than stopping and starting again at 30 what difference it might have made to her quality of life as part of her therapy and acceptance of things she cannot control for. I wanted to add this clinical vignette, with the patients permission, to bring alive some evidence of the positive impact on a patient with PKU that a drug like Kuvan can have, even though it is relatively small (3 exchanges to 6 is relatively small). I am also concerned that there is not enough evidence on why the cut off is chosen as a legal age of 18 when clearly there is ample evidence elsewhere in the literature that the brain continues to develop upto 25 years of age and 18 year olds are still in this development stage and ongoing education. So it does not make sense why the cut off chosen is 18 years of age and the evidence does not seem to draw on this important fact. To assume the adolescent brain is an adult one at 18 suggests that the evidence has not included the relevant scientific findings that has occurred over the last decade in particular with regards to brain development. In particular issues around learning, multitasking, stress and memory sleep and decision making are all affected in the adolescent years which is widely accepted now to take in the years upto 25 and it seems essential that Kuvan is continued during this period The highly accessible book the Teenage Brain by Frances Jensen (2015) is a good starting point to learn more about this issue. I'm most concerned about access for pregnant women and wondered about evidence for healthcare & quality of life costs of neurodevelopmental disorders (especially intellectual or learning disabilities and ADHD) . The proposed guidelines would remove access to Kuvan for pregnant women, the consequences of which for some women in the first 12 weeks of foetal development would be detrimental to the foetal development in this regard. In my clinical experience some women for various reasons are unable to get to a phe level that would be safe for foetal development . Sometimes these reasons have included mental health reasons, or learning difficulties but in these rare circumstances, through no fault of their own, they have never been able to manage to be on diet and take supplements so managing that when pregnant was an impossible task to expect. To obtain evidence of clinical cases when Kuvan has provided a comparatively safe phe level for optimal foetal development (that I am aware of but have not seen written evidence of here) seems an important relevant piece of evidence that needs considering .		
14					Are the recommendations sound and a suitable basis for guidance to the NHS?	I do not think that the recommendations for excluding pregnant women as sound and a suitable basis for guidance to the NHS I do not think that the recommendations for excluding young adults upto 25 years of age sound and a suitable guidance for the NHS I do not think that the recommendations for excluding all adults who might otherwise benefit from the reduction in stress and improvements to their mental health, anxiety levels and quality of life due to taking Kuvan to be sound and a suitable basis for guidance to the Nhs.	Yes	Inherited Metabolic Team , QEH, NHS

15					Has all of the relevant evidence been taken into account?	You say there is little evidence so I would say you haven't looked hard enough or at similar other conditions e.g. type 1 diabetes. The biggest comparable I can think of for your recommendations is taking insulin off an 18 year old diabetic.	No	
16					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	I don't see this as cost effective when adults with PKU who struggle to manage the 'most restrictive diet in the world' will be a huge cost burden on our services, such as mental health services as well as not contributing to their full potential to society in the form of tax payments etc. Short sighted recommendations that are just lip service.	No	
17					Are the recommendations sound and a suitable basis for guidance to the NHS?	Not at all as per all my comments	No	
18					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	Can't believe you are asking if there is any discrimination when age discrimination is in black and white!!!!! I'm surprised this isn't illegal what you're doing.	No	
19				I am a friend to a a mum and dad who are the parents of an infant with classical PKU. I am staggered by your recommendation to cap the usage of the drug at 18 years old. Especially given you then go on to say the brain develops until the age of 25. I am surprised my taxes go towards such contradictory evaluations. I fear for this boy when he turns 18 when this medication is stripped away from him. He will be accustomed to a more relaxed diet if he responds. On his 18th birthday, right at when he will be due to sit his A-Level exams, apply to university and so many more milestones at this stage, his life will be turned upside down. He will have to learn how to cope with what has been labelled 'one of the worlds most restricted diets' at a time when the symptoms will start to set in whilst at a stage of trying to gain independence. For my friends son, this is 17 years away, but my thoughts are with those who are teenagers - do they take the drug for a better few years, to then have their life turned upside down when they turn 18? I was also surprised to hear that the recommended maximum dose of 10mg/kg. The manufacturer has licence for up 20mg/kg. I can't think of any drug where the effective dosage is limited because of cost reasons. Many that would respond to this treatment won't because they are being given half a dose. Please give these children a fighting chance at unlocking their potential. Don't write them off. Doctors should have the FLEXIBILITY to prescribe the dosage as they see fit - some patients will need the maximum dosage of 20mg/kg, some will need 10mg or 5mg. It's correct the costing has been done on the average dose of 10mg because that it what it says: AVERAGE, not the MAXIMIUM. Basic maths are being thrown out of the window.			No	
20					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment,	Make available to anyone over the age of 18	No	

					pregnancy and maternity?			
21				This needs to be made available to everyone over the age of 18!!			No	
22					Has all of the relevant evidence been taken into account?	No	No	
23					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	No	No	
24					Are the recommendations sound and a suitable basis for guidance to the NHS?	No	No	
25					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	The recommendations as they stand are discriminatory on the grounds of AGE, DISABILITY, PREGNANCY and MATERNITY	No	

26	recommendations			I would like to provide some background information to my comments if that is possible. My son is 14 and has classic PKU. 3 years ago we took the decision to self fund Kuvan for a number of reasons as follows. 1) He suffered with terrible gastric issues which led to many days off school and caused him much anxiety and distress. We suspected this was down to the artificial nature of the diet, lack of natural protein that was offered by the number of exchanges he was on and lack of fibre. His gastric issues were also exacerbated by the foul tasting amino acid supplement he had to take 3 times each day. 2) On 8 exchanges we felt he was struggling food wise. 3)Despite being well controlled he had issues with cognitive function and concentration and struggled at school. 4) He experienced severe mouth ulcers on a regular basis which caused a lot of pain especially having to drink the acidic supplement which caused stinging and made him cry regularly. He takes less than half a dose (because that is what we can afford) As a result of taking kuvan his exchanges doubled. He now eats normal bread, rice, vegetarian foods and previously restricted foods such as cereals and potatoes in much greater quantities that fill him up. He only takes 2 amino acid supplements each day instead of 3. His gastric issues cleared up almost straight away and he has had one mouth ulcer since he began taking Kuvan. He is an extremely happy satisfied young man who now enjoys eating food. Most importantly for us however was that his concentration improved dramatically and he managed the stresses of senior school well. It is my opinion that if it hadn't been for Kuvan he would not be studying for 7 GCSE's. The huge impact Kuvan can have on someones life is severely underestimated. Why? Because not enough research and studies have been done to demonstrate this. Why? Because we are a rare disease. This drug has been available for 12 years and here we are still trying to justify its use. At this point I will use my experience as evidence as to why it is dangerous and unethical to remove treatment at the age of 18. My sons healthy diet would be withdrawn, his debilitating health issues would undoubtedly return as he would be forced back onto a synthetic diet and would have to return to maximum dosage of amino acid supplement. His concentration and clarity at the very time he needs it most would also be impaired as he attempts to follow a dietary regime which is alien to him. The difficulty in trying to adapt may well result in anxiety and depression at an age when there is so much going on in a young adults life (leaving home, university, first job). Removal of Kuvan at 18 is an extremely dangerous decision. I believe it would lead to all manner of complications.			No	
27	recommendations	1 Recommendations	they are under 18	I welcome the recommendation that Kuvan will be made available to children under 18 however it should be made available to all responders whatever their age. Furthermore it is both dangerous and unethical to stop this treatment at age 18. The reasons for this are summarised as follows and I will revisit this later on in my comments. 1) The brain is not fully developed at 18 so how can you justify stopping a treatment that will help protect the brain at this age? 2) By withdrawing treatment with Kuvan you are essentially removing food from that person and expecting them to live on prescription food which is inadequate and synthetic. Kuvan enables someone with PKU to eat a range of foods which are prohibited on the regime. This includes 'normal' bread/bread products, beans and pulses, rice, cereals, dairy such as yoghurts and vegetarian meat free alternatives to name but a few. It also allows foods to be eaten in greater amounts. For some people treatment with Kuvan allows even greater freedom with foods such as eggs and some meat being allowed. If you take Kuvan away that 18 year old will no longer be able to eat these things and will have to adopt the strict diet based on vegetables fruit and prescription foods. Something that person may never have experienced if they have been on Kuvan since birth or for many years if they are given access under your proposals at say age 14. This would be hugely challenging 3) Age 18 is a critical point in any persons life never mind someone with PKU. To take away treatment when you are possibly sitting important exams, at University, leaving home or getting your first full time job is unethical. Withdrawl of kuvan would lead to severe problems in the management of the condition and most definitely result in many not being able to adhere to the diet any more. They would come off diet and start to experience all of the symptoms I have seen in adults with PKU. This is a serious concern. I think it would also have implications for mental health.			No	
28	information-about-sapropterin	Price		It is common knowledge that Kuvan is or will be off patent soon in the UK and that there are other generic sapropterin drugs available and are awaiting approval. These generics are SIGNIFICANTLY cheaper than Kuvan. Had the committee appraised sapropterin based on the generic price it could have been available to ALL that benefit. Why wait until now to approve Kuvan. You have had 12 years. This doesn't make sense to me.			No	

29	committee-discussion	Recommending sapropterin for certain groups of adults cannot be justified given the cost-effectiveness estimates		I am unsure how the Committee could not justify use of Kuvan for adults with learning disabilities and also with autism. There are adults in the pku community with both and carers struggle terribly in trying to ensure adherence to the diet. In many cases non complaince with the diet exacerbates feelings, mood, behaviour etc. Must these people battle on with the immense negative impact up on their own health when life could be made much easier. There are adults with both diabetes and PKU. They will be very very small in number. I cannot begin to imagine how difficult it is to manage both conditions. Why wouldn't a Committee agree to fund Kuvan in this situation.			No	
30	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	However, adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25.	Yet you are proposing to withdraw treatment from people with PKU when they reach 18 years of age. This is a dangerous and unethical decision. It is also discriminatory.			No	
31	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	In adults, high Phe concentrations can result in short-term symptoms, which are considered reversible by lowering Phe levels through diet. These include impaired executive function, reduced autonomy, impaired social maturity, difficulty forming relationships and neuropsychiatric symptoms such as depression, anxiety and inattention.	These are all established serious side effects of high phe levels. Where is the evidence that these effects miraculously 'disappear' when you lower you levels. There is none. And even if there was this is assuming that an adult can stick strictly to the diet when there is a significant amount of adults are NOT keeping their levels below that which is required because they CAN'T because the dietary regime is just too challenging. What do you eat as an adult on say 6 exchanges of protein per day??? No meat no fish no eggs no dairy no pasta no bread no pulses no nuts/seeds. You can eat fruit, some vegetables and make things from prescription pasta or rice. If you are lucky your exchanges might stretch to 1 weetabix (2 exchanges) and 1 slice of shop bought bread (4 exchanges).			No	

32	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	Clinical experts estimated that 10% to 20% of patients struggle to maintain control of blood Phe levels	Where is the evidence for this? How do your clinical experts know this? I am not aware of any research. The figure is much much higher. The problem is much bigger for our community than your committee has been led to believe by your expert clinicians.			No	
33	committee-discussion	High blood Phe levels in pregnancy can have harmful effects on the unborn child	They noted that good control of blood Phe levels (below 200 micromoles per litre) should be maintained if possible,	I think your decision regarding the refusal to grant Kuvan for women who are planning to conceive or have conceived is by far the most shocking of all. We are living in 2021. A woman should not fear getting pregnant or suffer in doing so. Have you any idea how difficult it is to manage a diet so restricted in protein that your levels are below 200 micromoles per litre. At a time when you are most likely to be exhausted and have nausea/sickness. There are women with PKU who have chosen not to have a family because of this. Kuvan could reduce so much worry and anxiety and facilitate a safe, healthy and happy pregnancy. What price can you put on that??			No	
34	committee-discussion	People with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet	Patient experts explained that being on a strict protein-restricted diet is burdensome and demanding for people with PKU and their carers for several reasons:	I also think that adults struggle sticking to the diet because there are so few foods a person with PKU can eat. They can't go to reataurants, they cant just fancy a pizza or a burger. Food is essentially off the menu. It is disgraceful that there is a treatement available to adults with PKU that would enable them to eat so much more food that they are currently denied. That this treatment is available to those who respond (including adults) across the world but not in the UK makes me question if decision makers really understand the full extent of this condition. I don't think they do.			No	
35	committee-discussion	The costs of protein-restricted diet estimated by the company are reasonable, but the cost savings with sapropterin are uncertain	The committee concluded that the cost savings related to a reduction in protein-restricted diet are uncertain.	Can the committee not request additional information on cost savings so that you can be more certain?? Since taking Kuvan my 14 year old son has reduced his supplement from 3 to 2 each day. The range of foods he can now eat has meant that we no longer rely on prescription foods other than pasta when previously we received bread mix, cake mix, pku rice, pku burger mix. These would be at a significant cost!			No	

36	committee-discussion	The committee is unable to consider women who are pregnant or planning to conceive separately, and welcomes further comment and evidence on this group		I would like to ask if the Committee are aware of the UK Strategy for Rare Diseases which aims "to ensure no one gets left behind just because they have a rare disease". It also states that it must help pregnant women to eat well. Pregnant women with PKU do not eat well during pregnancy. They survive. As I have already stated I am saddened that the Committee did not deem a pregnant female with PKU (knowing what you now know of the difficulties in maintaining levels and the severe risks of disability to their unborn child) worthy of Kuvan. I am aware that NHS policy covers pregnant women who are unable to establish safe phe levels. This also saddens me. This NHS policy is very dangerous and runs the risk of a baby coming to significant harm. There is a drug (KUVAN) which should be given to women who respond full stop to help them manage their diet properly should they be thinking of becoming pregnant or becoming pregnant accidently. A female shouldn't have a life filled with anxiety at the prospect of becoming pregnant and then that child being born with extreme disability. Why in the year 2021 is not being given routinely to pregnant women? this I think is a scandal.			No	
37	committee-discussion	Sapropterin is not recommended in adults with PKU for treating HPA that has been shown to respond to sapropterin		To fund children and not adults is discrimination. The number of adults struggling to maintain levels has been HUGELY UNDERESTIMATED BY THE EXPERTS WHO HAVE GIVEN EVIDENCE HERE. Our adult PKU population have been messed around by the health system in the UK since PKU was first diagnosed. Some adults were told to come off treatment as small children others as young teens. Even in more recent years Consultants have and still are advising young adults to relax dietary treatment at some clinics. This is so contradictory. Many have relaxed their diet only to discover that they suffer from serious side effects. To return to diet has been a huge challenge and many find it impossible. Diet for Life was recommended in 1993 for PKU by the UK Medical Research Council who stated that blood phe for adults should be kept as low as that for children but if adults with PKU were struggling this must be no higher than 700 micromols/litre. The number of adults struggling to keep levels below this is far more than your experts have said. We just don't have the evidence because no one has bothered to do the research. Adults are suffering terribly because of their inability to keep levels down. I have come to know a great number of adults with PKU desperately wanting to adhere to the regime but can't. They have had huge difficulties completing education and holding down employment. This is a huge worry for me if my son were to be taken off Kuvan at 18. They also have feelings of anxiety and experience shakes and tremors when levels are out of range. Please realise it doesn't take much for levels to fall out of range!! An exchange too much one or two days a week!!			No	
38	committee-discussion	Sapropterin is not recommended in adults with PKU for treating HPA that has been shown to respond to sapropterin	there is no corresponding increase in quality of life to offset these costs,	I am unsure how the committee are able to conclude this. There is a HUGE increase in quality of life if it means levels are controlled in adulthood many of which I have mentioned. Here are just a few 1)The ability to eat a healthy varied diet 2)The ability to eat with family and friends (do not underestimate the impacts PKU has on social activities) 3)The clarity of mind and improved concentration that keeping low levels bring. This could lead to better education, job prospects, efficiency at work, promotion prospects etc 4)Better mental health as high levels bring on anxiety and depression. Improved outlook also results 5) Better physical health such as gastric issues which people on the synthetic diet report due to lack of natural protein How are these not considered better quality of life issues ALL as a result of being on kuvan.			No	
39				My daughter has been diagnosed with PKU we never even heard about it what shows how rare it is. It is an amazing news that our little one may be able to try kuvan. It would be life changing if she respond on it. However we feel absolutely devastating about decision to take it away when she will be 18 years old. How possible could she give up on food you already loves after so many years without having mental health problem or depresion. Also decision about only giving them maximum of 10mg/kg seems brutal what if they does respond but they need a bit more of kuvan? There is so many questions in our heads, how to manage so strict diet? How to explain that little girl that she can't have food that other kids can? How to make sure she not take something that she shouldn't when we won't be there? And there is much more... kuvan could possibly change her life for so much easier,and our life less stressful,but thinking of taking it away after years it make me just upset. Thinking of all teenagers who could finally have a bit of normal life by taking kuvan but only for few years?! As it all will be taking away... it's just not fair. Just try imagine your kids are in this situation. Please don't make money be more important then mental health, more normal life for all them people children and adults.			No	

40					Has all of the relevant evidence been taken into account?	Please see answer below	No	
41					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	Given the information provided this is difficult to evaluated.	No	
42					Are the recommendations sound and a suitable basis for guidance to the NHS?	I believe the recommendation for prescription of sapropterin for age <18 is sound, but failing to prescribe it to responsive adults >18 is not well motivated.	No	
43					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	I believe the recommendation is very negatively affecting women who are pregnant or planning a pregnancy. Generally, it is negatively affecting all adults who struggle to maintain good dietary control in spite of negative consequences for their aspirations, personal and family life.	No	
44				Recent published NICE guidelines recommend the prescription of sapropterin, in responsive people with PKU, up to 18 years of age. The possibility to prescribe sapropterin to children is well motivated and welcomed by people with PKU. It is unclear, however, why prescription is limited to people under 18 years of age. Evidence indicates that adults with PKU would equally benefit. There is strong evidence that even adults with PKU (AwPKU) who have been treated early and continuously suffer from cognitive impairments (Feldman et al., 2019; Weiglage et al., 2013; Palermo et al, 2017; Hofman et al., 2018). These impairments are widespread within the PKU populations and involve a variety of functions. There is a reduction in IQ (see for example, Moyle et al., 2007; Palermo et al., 2017; Nardecchia et al., 2015; Ris et al., 1994; Weglage et al., 2013), but also a reduction in some specific cognitive functions which are very important for successful management of work, personal and family commitments. These impairments involve what are collectively known as executive functions, including reductions in reasoning, flexibility and planning, sustained attention, visuo-spatial skills, visuo-motor control, and higher language skills (e.g., Bugard et al., 1997; Schmidt et al. 1994; De Felice at al., 2017; Jahjia et al., 2017; Channon et al., 2004; 2007; Moyle et al., 2007; Nardecchia et al., 2015; Palermo, 2017). Moreover, there is a significant reduction in speed of processing (for a review see Hofman, 2018). In a meta-analysis of published results (Romani et al. in preparation), we found that, on average, AwPKU suffer a reduction in cognitive performance of about half a standard deviation (for both IQ and independently assessed cognitive functions). This means that, on average, AwPKU lose about 20 places in a ranking of unaffected individuals. It is to be stressed, moreover, that this is, on average. Some individuals experience much more severe impairments curtailing their potential and aspirations. The committee recognizes that there is strong evidence that cognitive impairments in early-treated AwPKU are due to imperfect metabolic control (see Romani et al., 2017; Romani et al., 2020; Hofman et al., 2018). Evidence that metabolic control is important beyond adolescence is less strong because people who have maintained better control in childhood and adolescence are often the same people who maintain better control in adulthood. Thus, effects at different ages are difficult to separate. However, a number of results suggest that maintaining low Phe levels is also important in adulthood. First, for some cognitive functions, performance correlates more strongly with current Phe level than historical Phe levels (Romani et al., 2017; 2020). Secondly, there is evidence that cognitive performance, well-being, and quality of life can be changed within participants by modulating Phe levels. Studies have shown that cognitive performance can be significantly affected by changing Phe			No	

levels though pharmacological manipulation (e.g., ten Hoed et al., 2011), diet resumption (Anwar et al., 2013; Clarke et al.1987; Schmidt et al, 1996) or diet discontinuation (Lou et al., 1985; 1987; Cerone et al., 1999; but see Hogan et al., 1986 for no effect) and several studies have shown similar effects on psychological well-being (see Anwar et al., 2013; Bik-Multanowski et al., 2008; ten Hoedt et al., 2011; Gassio et al., 2003; for effects in late-treated AwPKU see also Dion, et al, 2001; Hoskin, et al., 1992; Marholin, et al., 1978). All these results support the claim that Phe levels can influence adult brains beyond adolescence.

Finally, the recommendation of prescribing sapropterin only up to 18 years of age is based on the statement that 'there is no risk of irreversible brain damage in the adult population'. One cannot claim that there is no risk. This is the first generation of adults with PKU to reach middle age. We do not know what effect on brain prolonged high levels of Phe will have. What we do know, however, is that the effects of high levels of Phe are similar to the effects of aging both in terms of neurophysiological mechanisms and in terms of behavioural effects. Both high levels of Phe and aging disrupt myelination and the availability of dopamine in the brain and produce similar patterns of impaired and spared functions: they both reduce processing speed, but do not accuracy; they both have stronger effects on visuo-spatial skills than language skills; and they both impair executive functions, but not consolidated knowledge, sparing functions like vocabulary, and spelling. Given these similarities it is certainly possible that the effect of high Phe and aging may interact in people with PKU leading to accelerated effects of aging on the brain and to an increase in the rate of dementia. Once these degenerative processes are triggered they will be irreversible.

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45	recommendations			This means that adults won't be able to have the drug and if a child who was receiving it would have to stop when turn 18. This is totally unfair.			No	
46	information-about-sapropterin	Marketing authorisation indication		Why are adults not being allowed the drug?			No	
47	information-about-sapropterin	Dosage in the marketing authorisation		The dosage is fixed but there should be flexibility so each patient gets the amount they need.			No	

48	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults		It seems that despite there being evidence that adults can have pku and have irreversible effects that they are being denied the drug.			No	
49	committee-discussion	High blood Phe levels in pregnancy can have harmful effects on the unborn child		It seems awful that if high blood phe levels in pregnancy can have harmful effects that pregnant women will be denied this drug.			No	
50					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	As a metabolic CNS I can see a few issues with the medication being stopped at 18 years of age. This will be difficult for all families and children to understand they are starting a medication that will be stopped because of the guidance. If we have eligible 13 / 15 year olds for the medication what will be the psychological effects on them knowing the medication will stop at 18 years of age. This is already a difficult time for them in their lives with other changes that happen e.g. schooling, friendships, alcohol.	No	
51					Are the recommendations sound and a suitable basis for guidance to the NHS?	No they lack evidence that is available for pregnancy PKU and Phe levels. They discriminate.	No	

52					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	Stopping at 18 years of age is discrimination based on age. Why is a child with PKU allowed Kuvan and an adult is denied this? They both have PKU. It is hard for all ages with PKU to follow the diet. Not providing Kuvan to pregnant women who respond to Kuvan is discrimination against women, pregnancy and maternity. Why wouldn't we want to promote a healthy baby? Why would we deny someone the chance to have a baby with optimum brain development. Wouldn't you want your baby to have the best chance in life? Make sure there is a robust programme for testing response to Kuvan so those who respond get benefit and there are cost savings. Make sure those who do not have a response are not using Kuvan as this is not cost effective. But make sure the dose is a range 5-20 so that it is optimised and individual. Many adults with PKU do have learning disabilities and they will not be able to respond to this guidance. They lack advocacy. They have fewer life choices because of their PKU. They live in more deprived areas, have less money and higher social and health inequality.	No	
53				I am a metabolic dietitian who has a wealth of experience with children and young people with PKU but also other patients with metabolic conditions requiring a low protein diet. A low protein diet similar to that for PKU. I have many issues with the draft guidance. 1. It is completely unethical to start a medical treatment in a child to then remove this at the age of 18 years. In my experience babies and children who start a low protein diet in early life do not know anything different than this. It can be difficult at times but they generally manage. They will still have high Phe levels that are damaging through illness and times when it is harder to manage their condition. What I do know for certain is that any child with any metabolic condition diagnosed later in childhood or teens finds it incredibly difficult to follow such a strict diet. Especially if up until that point they have enjoyed a very different diet. Can you imagine eating normal bread, as much pasta or rice or potato or cauliflower as you like all your life and then when you get to 18 and no longer can have Kuvan you have to change to medical foods. These are really nothing like regular food. You have to limit to 25g of chips or 60g of cooked rice or 55g of mashed potato for each 1g protein. You can only have 8g of protein each day. Go home and weigh these things out and compare to what you would usually eat. At 18 when you are going to university and need to have optimal brain function your Kuvan is stopped and you want to fit in with your friends and you've moved away from home. All of a sudden you have to learn a diet you never grew up with, you have to take amino acid protein subsitutes three times a day. You need to weigh all of your food. You struggle and your Phe levels rise. You get brain fog. You fail your exams. Your mental health declines because of high Phe levels. You drop out of university and don't reach your life potential. You cost the NHS lots of money for protein substitute, for mental health services for antidepressants. There are many adult PKU patients who are at massive disadvantage in so many areas of their life. We continue to fund drugs for obesity when many of these patients struggle to follow diets or regain weight. These patients cost huge amounts of money. Millions of people who are obese.			No	

				PKU is a rare disease with a relativelysmall patient numbers. Not everyone is responsive to Kuvan but those who are could really have a very different life. 2. The dose of 10mg/kg does not reflect what we have seen in trials. Some patients need more and some need less. It should be a range between 5-20mg/kg/d. To optimise effectiveness and save money on medical foods and protein substitute. 3. It is appalling that when women turn 18 and have been on Kuvan because they respond to it and are planning on having a baby that they would be denied continuing with Kuvan. There is huge amounts of evidence of the time brain damage in the foetus occurs and this is in the first 6 weeks of pregnancy. A women turns 18 and again it is a struggle to move back onto a restrictive diet and stop Kuvan because she can no longer have the prescription. This is discrimination against women. She plans on having a baby with her partner. Her Phe levels are high because it is very difficult to learn how to follow this restrictive diet when all her life she has not been on one. The Phe goes higher, the brain fog comes and she finds it harder and harder to follow the strict diet. The unborn baby who has no choice in this gets brain damage. They have delayed learning. They have costs on the NHS for speech therapy and additional learning needs. Vs she is able to continue Kuvan at 18. She goes to university and starts a job. When she has a baby her Phe is very well controlled. The baby's brain develops normally. The baby is born healthy and attends mainstream school and has a healthy life.			
54				This is an absolute joke. Fair play to the people under 18 but with all due respect, do their parents not just make their meals then anyway? I know mine did. I had to eat what I did and drink the supplements I did because it was all I ever knew! I am now a 29 year old woman with pku, currently pregnant with my second child, only allowed 1 exchange per day , during a national lock down and I tell you what, it is bloody hard work!!!! I am doing all I can but keep getting unexpected high levels and the effects that can have on my unborn baby are crazy! Why are you only thinking of under 18s and not the rest of us? I'm absolutely baffled!			No	
55					Has all of the relevant evidence been taken into account?	I am a close friend to a parent of a child who has severe PKU. I have read this guidance and I have been staggered at the lack of evidence you have looked at. You have looked at a handful of research studies but mostly claimed a lack of evidence. Evidence is there - LISTEN to the experiences of those with PKU and their carers. I have read this document and been amazed at how their experiences haven't been taken into account. The people writing these recommendations simply have no idea of what living with this condition is like. I see and hear from my friend what the PKU life is like. Every morsel of food and drink that passes through their sons life has to be weighed and logged. The energy that takes, wow. He is on 5g of protein a day. Bear in mind that around 15 peas equals 1g of protein. Listen to the voices of those with PKU from this consultation and change your guidance accordingly.	No	

56					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	No! Firstly, lets start with the dosage. You have claimed that for cost reasons you are capping the dosage at 10mg/kg, when the manufacturer has licence for up to 20mg/kg. In the US, you state that 20mg/kg is the universal dosage given and in Europe, the AVERAGE is around 13mg/kg. How on earth can you then cap the maximum at 10mg/kg????? I think the people doing this consultation need a lesson in maths and the difference between an average and a maximum. It is correct to cost this medication at 10mg/kg, because it is an AVERAGE i.e. some will respond to 5 or 10mg. However, some will need the full 20mg/kg dosage. By capping the maximum dosage, you are endangering the lives of children with PKU. You are not giving them the chance to respond. You are writing their lives off. Your guidance states that this drug is effective for children - then give them a chance to see its benefits. You wouldn't give half a dose of insulin for cost reasons, not at all. Just because PKU is rare, it does not mean you can cut corners and endanger children. Doctors need the FLEXIBILITY to prescribe the dosage as they see fit, which as I said may be at 5, 10 or 20mg, all based on how the child in question responds. Don't tie the hands of doctors. Don't put limits on the potential of these children.	No	
57					Are the recommendations sound and a suitable basis for guidance to the NHS?	As per above, no, many factors are flawed such as the dosage and the multiple factors of discrimination at play.	No	
58					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	An incredible question given you are demonstrating direct discrimination on the grounds of age and maternity. MY friends son will be expected to stop this drug at 18 years old, he will have to learn basically how to eat and cook again on a ridiculously complicated and strict diet. You will turn his life upside down on his 18th birthday. You will wreck his examination performance, his ability to go to university and live independently.	No	
59				I think that to start a treatment that is life changing and then withdraw it at the age of 18 is unethical. The effect it will have on the mental health of the patient will in itself then become a problem for the NHS. If the dose of 10mg is not sufficient to gain control of PKU and a bigger dose would be, to deny this treatment would again appear unethical. The mental health of this cohort of patients would inevitably be affected.			No	

60	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	However, adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25. In adults, high Phe concentrations can	This contradicts your decision to stop the treatment at 18			No	
61	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	In adults, high Phe concentrations can result in short-term symptoms, which are considered reversible by lowering Phe levels through diet	again a contradiction to the decision tostop treatment at 18			No	
62	committee-discussion	High blood Phe levels in pregnancy can have harmful effects on the unborn child	The committee concluded that high blood Phe levels in pregnancy can have harmful effects on the unborn child. Early control of Phe levels, ideally before conception, would reduce the risks.	If the patient was already on sapropterin, this would eliminate the risk to the unborn child.			No	

63	committee-discussion	Sapropterin is clinically appropriate and beneficial for people with PKU that responds to sapropterin	Patient experts advised that adults with PKU who have taken sapropterin report improved day-to-day functioning, particularly concentration and mood. In addition, they were able to resume other activities such as studies or work. Parents of children with PKU report similar benefits in the mood, energy, concentration and behaviour of their children. They also report large increases in natural protein consumption, with children having a wider and more socially normal diet and greater freedom to participate in social activities. In addition, sapropterin also led to health benefits in children. These included increased bodyweight and growth, improvements in gastrointestinal symptoms and fewer mouth ulcers. Carers of people with PKU reported a significant easing of burden of care. This included not needing to prepare special prescribed low phenylalanine foods and being able to delegate childcare to others for first time. Some carers reported being able to return to work or study, increase working hours, spend more time with other children, and have time for other family responsibilities. The committee concluded that sapropterin is beneficial for those people with PKU that responds to sapropterin.	the above benefits to these children are well observed by any parent/ grandparent/family member. It does not make sense to withdraw treatment and deny over 18's the same benefit.			No	

64	committee-discussion	Long-term brain damage in children is an important aspect of PKU, but there is little evidence to estimate its effect on quality of life	The committee concluded that long-term brain damage is an important aspect of PKU, but there is little evidence available to estimate its effect on the quality of life of people with PKU.	Is there any plan to research this lack of evidence?			No	
65					Has all of the relevant evidence been taken into account?	I do not believe so	No	
66					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	Not necessarily - all evidence has not been considered and it appears that the main point is cost	No	
67					Are the recommendations sound and a suitable basis for guidance to the NHS?	No	No	
68	committee-discussion	Recommending sapropterin for certain groups of adults cannot be justified given the cost-effectiveness estimates	The committee considered that a positive recommendation for children but not adults was appropriate based on differing disease risk and cost-effectiveness estimates	Given that the impact on society of these groups if they do not have access to the drug over the age of 18, this should be enough to warrant access			No	

69	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	To avoid long-term brain effects in children with PKU, current treatment in the NHS consists of a protein-restricted diet and dietary supplements to control blood Phe levels. This diet should be continued as an adult. Clinical experts noted that poor control of blood Phe levels during childhood and irreversible long-term brain damage can then mean adults have a limited ability to control blood Phe levels through diet. One patient expert confirmed that there are adults with PKU in the National Society for Phenylketonuria (NSPKU) who have severe symptoms and irreversible brain damage. Clinical experts explained that brain development peaks at around age 12.	Again i think that people over the age of 18 are still vulnerable.			No	
70	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	This diet should be continued as an adult. Clinical experts noted that poor control of blood Phe levels during childhood and irreversible long-term brain damage can then mean adults have a limited ability to control blood Phe levels through diet.	This is evidence enough to show that adults should be given access to the drug over the age of 18			No	

71	committee-discussion	The sapropterin dose used in clinical practice in the UK would be lower than used in the PKUDOS registry and in line with European practice	The ERG was concerned that the doses of 10 mg/kg and 12.5 mg/kg for children and adults as suggested by the company are underestimates of the doses used in clinical practice. In KAMPER, the average sapropterin dose was 12.7 mg/day and this included 83.5% children under 18 (see section 3.8). In the PKUDOS registry the average dose was 18.7 mg/kg and around 60% of patients were under 18 (see section 3.8	why are the figures so different?			No	
72	committee-discussion	The costs of protein-restricted diet estimated by the company are reasonable, but the cost savings with sapropterin are uncertain	The committee noted the high annual costs of protein-restricted diet for each group (£10,326 to £15,973). The company suggested that there would be cost savings with sapropterin, based on a 71.2% reduction in the need for low-protein foods and supplements. While the ERG considered that the total costs of protein-restricted diet calculated by the company are reasonable, it did not consider the evidence for a 71.2% reduction to be robust (see section 3.11). The ERG produced 2 scenarios with 0% and 71.2% reductions. The committee concluded that the cost savings related to a reduction in protein-restricted diet are uncertain.	The cost effectiveness should be enough to accept that the drug should be available for over 18's			No	

73	committee-discussion	The committee is unable to consider women who are pregnant or planning to conceive separately, and welcomes further comment and evidence on this group	However, it was mindful of the importance of avoiding permanent damage to the unborn child and recalled what it had heard about current suboptimal management in the NHS	This should be enough of a risks to ensure the drug was available to pregnant women over the age of 18			No	
74	committee-discussion	Sapropterin is not recommended in adults with PKU for treating HPA that has been shown to respond to sapropterin	The costs of sapropterin are higher in adults than in children, but there is no corresponding increase in quality of life to offset these costs, and there is no risk of long-term brain damage in	I believe that the long term costs of not supplying the drug would outweigh any financial cost			No	
75				Firstly, its disappointing that you only gave 3 weeks to comment. 2) Why are the references in the 600+ document written in two formats, numbered and by authors surname and year of publication - this just confuses people. 3) The most important organ in the body is the brain 4) the brain develops throughout life, this does not stop at aged 18, 5) preventing someone from developing their brain into their full potential when there is something available to help PKU patients of all ages is wrong. 6) you are assuming 25% will respond but the actual numbers maybe lower, 7) why is NICE not building up a complete and thorough database, but gene sequencing PKU PAH gene to see at least if you only allow those up to 18 to have kuvan, to find out which mutations respond, then apply this knowledge to those over 18. 8) why not allow those over 18 to be able to trail kuvan for a month or so to see if they respond, that way more actuate numbers of how many respond can be calculated, and again sequencing their PAH gene at the same time, can allow the results be added to a database. 10) In summary a price on the development and continued development of a persons brain cannot be put, therefore if we know kuvan can help some PKU patients, then give it to all PKU now. Their improved cognition and therefore improved careers and salaries, may end up contributing more back to society and indeed HMRC than not being treated.			No	
76	recommendations	1 Recommendations		I'm so grateful for the approval of a treatment for PKU, using Kuvan. However, I am really disappointed and concerned by some of the limitations that have been put in place. The 10mg/kg dosage cap is not going to be adequate for a lot of sufferers, and if the dosage is not high enough and not totally effective, it could cause them to be categorised as a non-responder (incorrectly!) and then they'd have their access to this treatment taken away. Without this treatment, PKU sufferers will continue to face daily risks to their health. Clinicians should have the flexibility to dose as required, on a patient by patient basis. This is the common practice in a lot of other countries that are already using Kuvan as PKU dietary management. If a revision was made, to allow 5-20mg/kg dosages (these are the manufacturers' approved dosages) it would enable safer, personal management, where the dosage was aligned with the individual person's needs. Also, by removing access to treatment at 18, PKU sufferers will find themselves in an awful situation, where they are having to all of a suffen adapt to a very restrictive diet again, after years of management helped by Kuvan. PKU is a lifelong issue, it does not disappear with age. Adults should also be given acces to Kuvan, to help them manage their diet effectively and impact their quality of life positively. It has been shown that PKU can have terrible side effects, including (but not limited to) depression, anxiety and memory loss. I hope that this approval will be revised, to take into consideration PKU sufferers of all ages, as well as a removal of the 10mg/kg cap. It's great to see this			No	

				drug becoming accessible, but it would be fantastic to see those restrictions lifted, to help impact so many more lives.				
77				My granddaughter who is 15 weeks old was born with PKU although I'm grateful she will be able to have the drug Kuvan I think to take it away when she is 18 is ridiculous. This is the time when people are making big changes to their lives university, own house etc they will need Kuvan then not more upheaval in there life			No	
78					Has all of the relevant evidence been taken into account?	We have concerns regarding the intention to discontinue Sapropterin treatment at 18 years. Phenylketonuria (PKU) / Hyperphenylalaninemia is primarily a neurodevelopmental disorder. Maturation of the brain does not stop at 18 years but continues into young adulthood – with studies showing that structural brain maturity, the development of executive functions and social cognition is reached later than the end of adolescence (Blakemore & Choudhury, 2006; Sowell et al., 2001; McGivern et al., 2002; Monk et al., 2003). Impairment of executive functions is reported in some adults with early-treated PKU and we suggest treatment to attempt to prevent this should be continued until at least brain maturation is complete. 18-25 years is a critical period in many young adults' lives. It coincides with major events such as the end of schooling, state examinations, entry into higher level education and/or employment and more independent living. To withdraw Sapropterin from a young adult at 18 years therefore will result in that young adult being forced to make a difficult choice between accepting worsening metabolic control (with higher plasma phenylalanine concentrations) or adopting a more restrictive low protein diet (with an increased requirement for PKU amino acid supplements) to maintain their phenylalanine concentrations within recommended targets. In our experience, introducing a more restrictive diet after early childhood is extremely challenging and not well tolerated by young adults. Introducing and monitoring a change in treatment (with an increased requirement for medical and dietetic appointments, and phenylalanine bloodspot measurements) at this stage in life will be disruptive and potentially distressing for young adults – with a risk of long-term impact on health and social outcomes. To protect the maturing adolescent / young adult brain and avoid a significant change in treatment at 18 years, we suggest that NICE consider increasing the recommended age of treatment with Sapropterin to at least 25 years.	Yes	British Inherited Metabolic Disease Group (BIMDG)

79					Are the recommendations sound and a suitable basis for guidance to the NHS?	NICE has not given any recommendations on how Sapropterin-responsiveness should be determined longer-term. It is important that clear guidance is given. NICE may wish to look at the proposed pathway in the 'Interim Clinical Commissioning Policy: Sapropterin for phenylketonuria (All ages)'. Although many patients in the UK are not currently genotyped, data regarding the determination of Sapropterin-responsiveness by PAH genotype is also increasing (see http://www.biopku.org/home/biopku.asp). The specialist metabolic centres and the BIMDG suggest that a clear national consensus on criteria for responsiveness testing, priority groups for testing, monitoring guidance, and criteria for ongoing treatment should be developed.	Yes	British Inherited Metabolic Disease Group (BIMDG)
80					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	We have concerns that Sapropterin is not being offered as a first line treatment to women with PKU / Hyperphenylalaninemia who are planning a pregnancy and whose condition is Sapropterin-responsive. Untreated hyperphenylalaninemia in pregnancy is a highly teratogenic condition. Women with PKU / HPA in the UK who are currently planning a pregnancy need to adher meticulously to dietary restrictions in order to maintain phenylalanine concentrations within recommended targets and prevent the maternal PKU syndrome in their children. The economic cost of the maternal PKU syndrome has not been formally evaluated but these children have a spectrum of disabilities including intellectual disability, specific language impairments, attention deficit hyperactivity disorder, autistic spectrum disorders and congenital cardiac disease. The lifetime cost for the management of an autistic spectrum disorder with intellectual disability in the UK is estimated to be $2.2m, while the cost for an autistic spectrum disorder without intellectual disability is estimated to be $1.4m (this includes costs of health, social and educational services, lost employment and caregiver time costs)(Rosse & Janssen, 2019). Currently the first-line option for women with PKU / HPA is a protein-restricted diet with PKU supplements. However, a significant proportion of women will develop nausea and vomiting of pregnancy – which impairs their ability to tolerate unpalatable PKU supplements. At present Sapropterin can be offered as a second-line treatment to women in pregnancy (but only after standard PKU dietary measures have 'failed'). This is usually several weeks-months into pregnancy – at which point an avoidable prenatal insult may already have occurred. There are an average of 50 babies born per year to women with PKU. Based on the estimated prevalence of Sapropterin-responsiveness in the general PKU population, we estimate that approximately 9 of these women (and their babies) might benefit from the use of Sapropterin in pregnancy annually. In our experience, certain vulnerable groups of women are most at risk of difficulty managing dietary treatment in pregnancy, namely those with mental health conditions, learning difficulties, and/or affected by domestic violence. Women from this group, if	Yes	British Inherited Metabolic Disease Group (BIMDG)

						they are Sapropterin-responsive, would particularly benefit from access to treatment in the pre-conception period. Data indicate clearly that use of Sapropterin in pregnancy is safe and prevents the maternal PKU syndrome (Feillet et al., 2014; Grange et al., 2014). We suggest that NICE change their recommendation to allow all women of child-bearing age (14-45 years) to be assessed for Sapropterin responsiveness – and those who are responsive to be offered Sapropterin as a first-line option when they are actively planning pregnancy (the pre-conception period) and for the duration of pregnancy.		
81				The BIMDG welcomes NICE's recommendation for treatment with Sapropterin for children – and the associated benefits for parents and children with reduction in the need for a protein-restricted diet.			Yes	British Inherited Metabolic Disease Group (BIMDG)
82					Has all of the relevant evidence been taken into account?	The manufacturer's authorisation ranges from 5mg/kg to 20mg/kg, allowing for individualised prescription - a common practise already followed in many other countries. There are many patients in need of a higher dosage than 10mg/kg and the capping of the dosage leaves a high risk of no response. There is evidence that the brain continues to develop after the age of 18. For the prescription to finish at this age means severely restricting the quality of life for PKU suffers, particularly if the regular administering of saproterin were to be cut off suddenly.	No	
83					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	The costing of 10mg/kg is appropriate, however, the decision of dosage should be left up to the clinicians who have deeper knowledge of the individual's needs.	No	

84					Are the recommendations sound and a suitable basis for guidance to the NHS?	The dosage of sapropterin needs to be reviewed in order to allow a higher number of patients to be treated. The prevention of prescription to anyone over the age of 18 also needs to scrapped to ensure all sufferers of PKU are able to access this vital drug that helps them to manage their diet and lifestyle. The NHS needs to allow clinicians to use their judgement.	No	
85					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	Clinicians should be granted the ability to administer prescriptions on an individual basis - no one person is the same. The dosage offered is very restrictive. Many sufferers of PKU will still be at high risk and will have no response unless a higher dose is allowed. Therefore, although the approval of this drug is welcomed, the restrictive dosage will still be ineffective for many sufferers. PKU is not merely a childhood condition that automatically disappears at the age of 18. To approve a drug to help with the condition during childhood, only for it to be taken away once they reach 18, would a huge disadvantage - particularly at a key stage in life when suffers of PKU would be reaching adulthood and would need more support with management and consistency of their lifestyle and diet.	No	
86				Although the approval of sapropterin for PKU sufferers in the UK is very much welcomed, it seems the guidance stipulated is very restrictive to those who will need it. More needs to be done to ensure patients will be able to manage their condition whilst living a better quality of life. Also, the cap of 10mg/kg provides severe limitations for some - clinicians should be given the flexibility to prescribe the right dosage based on the individual's needs. Ultimately, the dosage should be left up to the clinicians who know their patients and can make the best judgements based on the individual's needs.			No	
87					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	Age needs to be looked at and pregnancy	No	
88				It says that it is only available for children until 18, surely if this helps them to have a better quality of life they need to continue taking it. It also states that brain development continues until 25 so surely if they come off the drug at 18 and are unable to manage the levels by diet alone this could cause serious harm. It also says about a fixed dose of 10mg but there needs to be more flexibility in this as it says doses between 5-20mg are recommended so needs to be worked out accurately so that everyone gets the quantity they need. The report also says about pregnant women having high PHE levels can lead to their babies having impaired growth, impaired intellectual ability and birth defects so why can't women who are planning on starting a family have this too.			No	
89					Has all of the relevant evidence been taken into account?	Yes	No	
90					Are the summaries of clinical and and cost effectiveness reasonable	Yes	No	

					interpretations of the evidence?			
91					Are the recommendations sound and a suitable basis for guidance to the NHS?	Yes	No	
92	recommendations	1 Recommendations	a dose of up to 10 mg/kg is used	Sapropterin is provided as 100 mg tablets. The SPC states that the calculated daily dose based on body weight should be rounded to the nearest multiple of 100. The SPC states 'for instance, a calculated dose of 401 to 450 mg should be rounded down to 400 mg corresponding to 4 tablets. A calculated dose of 451 mg to 499 mg should be rounded up to 500 mg corresponding to 5 tablets'. Using an example of say a child of 27kg, their dose would be 270mg, rounded up to 300mg. The rounded up 300mg would actually work out at 11.1mg/kg so above the 10mg/kg threshold. However, this is what is recommended in the SPC - would this be funded under the TA? Does the bullet point need making clearer with regards to this?			Yes	Medicines team at NICE
93					Are the recommendations sound and a suitable basis for guidance to the NHS?	Absolutely not	No	
94					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	Probably all of the recommendations! You are actively discriminating on the grounds of both age and pregnancy/maternity. To have the cheek to ask this question....	No	
95	recommendations	1 Recommendations	they are under 18	Kuvan should be approved for all age groups. It should not be limited to just those under 18. This guidance underestimates the benefits of Kuvan treatment for adults with PKU. It says there is no risk of permanent brain damage after the age of 18, but this is directly contradicted by the statement that the brain continues to develop up until the age of 25. More recent evidence shows that brain development continues to develop well into old age. Many adults with PKU have very serious symptoms – such as depression, anxiety, brain fog and memory loss - caused by high phenylalanine levels. Protein allowance does not typically increase as patients get older and therefore dietary treatment and management only gets more difficult in adulthood. The NHS has also sine 1993 recognised and endorsed that dietary treatment is for life. PKU is not cured once a person turns 18. The draft guidance does not stipulate or consider the impact on a patient taking Kuvan in childhood and then having it withdrawn on their 18th birthday. These 18-year-olds are often at a crossroads in their lives at this point, for example going to university or leaving home. Managing phenylalanine levels with dietary treatment alone is very difficult, especially for teenagers. 18-year-olds accustomed to a relaxed diet through using Kuvan would not have the coping skills and tools to switch to an extremely restricted diet and would go on to suffer a whole host of issues and symptoms. This issue has been completely ignored in the guidance.			No	

96	recommendations	1 Recommendations	a dose of up to 10 mg/kg is used	Draft guidance says “a dose of up to 10 mg/kg is used”. This cap should not be in place. Clinicians should have the flexibility to prescribe the dosage according to individual patient needs and in line with the manufacturers authorisation which ranges from 5mg/kg to 20mg/kg. With this current guidance, there is a large risk that many patients would be classified as non-responders, when they in fact need the higher dose of 20mg/kg. This is the common practice in other countries. The costing against 10mg/kg is appropriate as that is likely to be the average dose, but clinicians need the flexibility to prescribe up to 20mg/kg where required. The decision to cap the dosage is purely a cost reason, not a clinical decision. All other countries don’t have this cap, so why is the UK recommending this?			No	
97				My friends little boy has PKU and it has completely taken over their lives. It isn’t just about diet control, it impacts children and people on such a wider scale. Things that we take for granted like birthdays (party food, birthday cake), going out to places and just grabbing some food while your out or going for a family meal. The diet is restrictive and impacts individuals social and emotional well being. On top of that causes a great amount of stress on parents. The risk of brain damage. I do not understand why it has taken so long for this drug to be made available. However the restrictions are ridiculous. You have a drug that can make such a different to peoples lives but then money is more important than that obviously?! This drug will allow lots of children much more freedom in their diet and might mean that he even has a free diet! The draft policy is flawed! 1. It says that Kuvan can only be used by under 18s. This means that no adults can have it and anyone who starts using it as a child will have it revoked at 18. That is outrageous! How can you expect someone who has had a drug that controls their pku condition to them manage without it after using it for 18years!! 2. There are contractions in the policy. E.g women who want to be/ are pregnant don’t need Kuvan. In another part of the report it says that out of range levels in pregnant women can cause foetus defects. It is a terrible report. 3. The dose is fixed to 10mg. The recommended dose is between 5-20mg. We need flexibility so that each patient gets the amount that they need. Otherwise it is pointless, you need to give people what they need!			No	
98					Has all of the relevant evidence been taken into account?	No. The transition from child to adult at 18, when treatment is proposed to be withdrawn, needs to be studied and considered, including likelihood of adhering to an unaccustomed restricted diet and the level and severity of symptoms NICE consider acceptable. How many patients are likely to need 20 mg/kg, and how does that impact the financial business case? BioMarin indicate the 20 mg/kg is required in some patients.	No	
99					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	Possibly, but there is evidence missing.	No	
100					Are the recommendations sound and a suitable basis for guidance to the NHS?	No. Few parents will accept relying on Kuvan for their child's wellbeing and lifestyle for it to be withdrawn as soon as they reach 18 years old. It is a life-long condition, requiring cradle to grave treatment.	No	

101	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	This diet should be continued as an adult.	The reason the diet needs to be maintained is that PKU affects both children and adults. It could be argued that it is harder for adults to remain on diet with the work pressures, social and relationship pressures.			No	
102	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	Clinical experts explained that brain development peaks at around age 12. After this high Phe levels are unlikely to affect IQ.	IQ is a limited measure of life's impacts. Surely more relevant is the persons emotional intelligence (EQ) and wellbeing - there is no doubt that this is impaired well beyond 12 and into adult life			No	
103	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25	If this is the case, then stopping treatment at 18 doesn't have foundation			No	

104	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	In adults, high Phe concentrations can result in short-term symptoms, which are considered reversible by lowering Phe levels through diet. These include impaired executive function, reduced autonomy, impaired social maturity, difficulty forming relationships and neuropsychiatric symptoms such as depression, anxiety and inattention.	Symptoms can be lowered "through diet" in children as well as adults, so this rationale cannot be used just in adults. It misses the main point - Kuvan will allow the relaxation of diet, and facilitate a more normal life.			No	
105	committee-discussion	People with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet	Clinical experts noted that just over 50% of adults with PKU are on a protein-restricted diet, while about 30% of adults have stopped their diet and the other 20% have difficulties maintaining it.	This contradicts earlier commentary that adults can simply manage their diet to relieve the adverse effects of PKU. Evidence suggests adults find it increasingly difficult to stick to a restricted low protein diet			No	
106	committee-discussion	The sapropterin dose used in clinical practice in the UK would be lower than used in the PKUDOS registry and in line with European practice	The company stated that the mean dose of sapropterin for children is 10 mg/kg and the mean dose for adults is 12.5 mg/kg	If these are the mean doses, this is how, on average, Kuvan would be required if made available to all. Some will respond well to doses of say 5 and others will need 20. By limiting the maximum to 10 mg/kg, the committee is missing the understanding of averaging, and as a result those relatively small number of people needing 20 mg/kg will be discriminated against			No	
107	committee-discussion	The sapropterin dose used in clinical practice in the UK would be lower than used in the PKUDOS registry and in line with European practice	One clinical expert stated that in their experience using between 10 mg/kg and 20 mg/kg resulted in little difference in outcome. Clinical experts further explained that increasing sapropterin dose does not improve efficacy because response to sapropterin primarily depends on the level of PAH activity and mutations, not the dose.	That is not our experience. We have 2 boys that undertook the one month Kuvan trial. At 10mg/kg the impact was reasonable, but when this increased to 20mg/kg the change was dramatic. Pre Kuvan my son's level was measured at 607, with 10 mg/kg it went down to 349, but when moved to 20mg/kg the level fell to 145.			No	

108	committee-discussion	Sapropterin has not been shown to be cost effective in adults with PKU	The committee noted that the company's base case for adults was also above the cost-effectiveness range.	Does not take into account the adverse impact of withdrawing treatment at 18			No	
109	committee-discussion	Sapropterin has not been shown to be cost effective in adults with PKU	Therefore, costs of sapropterin are much higher in adults than children; but there are no corresponding increases in quality of life to offset these costs.	This analysis ignores the need for continuity when a child becomes an adult, and maintaining the quality of life the child has become used to. By taking away the treatment at 18, the already low adult adherence to diet will become near zero (increasing all the quoted adverse symptoms). Preventing permanent brain damage is only one part of the rationale for Kuvan.			No	
110	proposed-date-for-review-of-guidance	5 Proposed date for review of guidance	NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date.	With a "generic" product now expected, which will be cheaper has Kuvan, can we expect this revised costing to be considered and the recommendations updated once this now produced t is launched?			No	
111				This is disgusting development. We have waited 11yrs to be told this. My son is 15 & why would any sane parent start their child on a drug to be withdrawn at 18, if it makes a difference that's cruel. I have few wordsbut this descrimimates against alot of other people - selective treatment is shameful!!			No	
112					Has all of the relevant evidence been taken into account?	The data on the UK adult PKU population may not have captured the data from all centres. We have one of the larger centres in the UK and we have audited our PKU clinic patient populations internally and have presented the data in abstract form as well as via a medical student QPEP report submitted in 2019 to the University of Manchester (see below):- (Dr) George Altman 2019 Word count: 3990 (excluding references and appendix) Quality improvement report using HADS, BECKS and a retrospective audit to monitor mental health symptoms for PKU in a large single UK centre Abstract Recently published NSPKU European guidelines have recommended a lifelong diet with Phenylalanine(Phe) control below 600mmol/L for Phenylketonuria(PKU) patients. A literature review found that evidence for this recommendation is drawn from a low number of mainly observational studies, the only randomised control trial had a small number of participants and therefore a high risk of selection bias and type 1 error. In addition, the studies have taken place on American and European populations without consideration of differences in the UK population. This audit combined data from two previous audits and used HADS/BECKS questionnaires to gather prospective data on mental health symptoms in the PKU population. Our finding was that patients with a 2-year average phenylalanine level of >600mmol/L were significantly more likely to have a diagnosis of low mood. Patients with Phe >600mmol/L showed a trend of being more likely to have depression, anxiety and mood swings but this was not statistically significant. In addition, there was a high prevalence of anxiety and depression in the PKU population.	Yes	National Society for PKU as well as Salford Royal NHS Foundation Trust

Each method gave a different estimation of depression prevalence: retrospective audit (14%), BECKS (54.2%), HADS (14.8%). Furthermore, it was found that 82% of non-pregnant patients are not adhering to guidelines on Phe control.

Introduction

In 2017 the NSPKU European guidelines were published, the recommendation for lifelong control below 600mmol/L was given(1). The evidence was graded at a D, therefore further studies are required to improve the strength of evidence for this guideline. The original 2017 audit aimed to evaluate the validity of this recommendation by assessing the prevalence of mental health symptoms in patients adhering and not adhering to these guidelines. Limitations in the method were identified and it was recommended that prospective research was carried out using HADS and BECKS validated questionnaires.

PKU is an autosomal recessive inherited metabolic condition. Patients with the condition have a deficiency in phenylalanine hydroxylase(PAH)(2). The deficiency in PAH results in high Phe levels in the blood. High Phe is hypothesised to disrupt neurotransmitter (serotonin and dopamine) metabolism(3). In the UK, an estimated 1 in 10,000 newborn babies will have PKU(4). Currently, the only treatment available for PKU in the UK is a life long Phe restricted diet(5). It is estimated that half of all PKU patients have been lost to follow up, this means there may be many patients no longer on the diet who are only receiving care from their GP. It is important to determine the impact of high phenylalanine on mental health diagnoses as there may be a considerable burden of mental health disease in this population which is not being recognised. It is possible that as PKU may alter serotonin metabolism this could potentially attenuate the response to selective serotonin reuptake inhibitors (SSRIs) due to reduced availability of serotonin, therefore SSRIs may not be as effective in PKU patients.

Aims

The main aim of the audit was to identify if mental health conditions(depression, anxiety, low mood and mood swings) are a significant health issue in the Mark Holland metabolic unit PKU population. In particular: are patients with PKU at greater risk of mental health diagnoses if their average phenylalanine level is greater than the NSPKU European guidelines of 600mmol/L?

Further aims of the audit were:

1. Continue an Audit loop and identify how it can be repeated and improved
2. Evaluate the effectiveness of the current database system for the storage of patient data
3. Identify areas of opportunities and barriers to future research
4. Assess the frequency of monitoring of Phe levels in comparison to NSPKU guidelines
5. Assess the compliance with European guidelines relating to recommended adult Phe levels
6. look for evidence to support or dispute the NSPKU European guidelines – “In treated patients with PKU aged 12 years or older,

the target phenylalanine concentrations should be 120–600 µmol/L."(1) (p.743)

Key measures for improvement

1. An increase in the number of patients under the 600µmol/L guidelines for Phe control

Literature review

Objectives
The scope of the literature review in terms of population will include adult patients with a diagnosis of PKU. The exposure of interest is average Phe level above 600mmol/L, in comparison to patients with an average Phe level of less than 600mmol/L. The outcome that will be measured is the prevalence of mental health diagnoses in this population (Focusing primarily on low mood, anxiety, depression and mood swings). Studies which have been published in the last 30 years investigating the relationship between phenylalanine levels and mental health diagnoses will be included in the literature review. A detailed appraisal of each paper was undertaken but only the appraisal of the randomised control trial is included in order to adhere to word limits. The types of studies to be included will be RCT's and retrospective studies.

Search strategy
The search strategy involved a database search using a scoping review. Boolean logic was used to combine keywords: Depression, Anxiety, Mood, PKU, Phenylketonuria, Phenylalanine. Three databases were used Pubmed, Google scholar and University of Manchester library. Citation chaining was also used to find additional papers.

The outcome was that 18 papers were identified. 12 were rejected as they did not meet the criteria for inclusion (4 were types of studies outside the inclusion criteria, 3 used a different population, 2 measured a different outcome, 3 measured a different exposure)

Description of studies

Overall 6 papers met the search criteria(6-10). In terms of validity, there was a wide range of study designs. All studies suffered from having a low number of participants increasing the risk of type 1 errors. In terms of reliability, two studies found a significant relationship between Phe levels and neuropsychiatric symptoms, one study found a non-statistically significant relationship and three studies found no relationship. In terms of applicability, none of the studies was carried out in the UK which is a significant limitation.

Appraisal of: High phenylalanine levels directly affect mood and sustained attention in adults with phenylketonuria: a randomised, double-blind, placebo-controlled crossover trial

Appraisal

The first paper considered was High phenylalanine levels directly affect mood and sustained attention in adults with phenylketonuria: a randomised, double-blind, placebo-controlled, crossover trial(11). The CASP format is being used for appraisal of the paper.

Validity

The trial clearly focused on the research question by measuring the impact of the exposure (Phe levels) on a similar outcome (profile of mood states questionnaire) in an adult PKU population. The assignment of patients was randomised, double-blinded and carried out by an independent data manager. All patients who entered the trial were accounted for, 12 patients were originally recruited with 3 patients withdrawing for documented reasons. Patients, health workers and study personnel were blind to the treatment. The patient groups were similar at the start of the trial with slightly more females taking part 6/9, a range of ages 19-34, and all patients having a Phe level below <1,100 µmol/L. The groups were treated equally as this was a cross over trial with both groups receiving the placebo and intervention. There is a risk of uptake bias as only 9 of 129 eligible patients agreed to participate. Therefore, the group of patients who agreed to participate may not represent the PKU population.

Reliability

In terms of reliability, the relevant outcomes measured include self-reported mood states and self-reported depression as measured by the POMSr questionnaire. The study found that self-reported mood states "… were significantly less favourable during the Phe-loading period compared to the placebo period ($p = 0.017$)."(11)(p170). Post- hoc analysis was also used to suggest patients felt more depressed "(trend, $p = 0.097$, $\eta p2 = 0.31$, power = 0.38)"(11)(p166), however, this P value is not >0.05 and therefore is not significant. Treatment effect size and confidence intervals are not provided so it is not possible to comment on the size or precision of the estimated treatment effect.

Applicability

The results can be applied to the Salford population with caution, although they represent European adults with PKU, the possibility of uptake bias making the sample unrepresentative should be considered. The trial population differ as the age is younger on average compared to the Mark Holland Metabolic unit PKU population and the range of phenylalanine is lower (<1100). All clinically important outcomes were considered.

Limitations of the literature

The limitations of the current literature on the relationship between Phe levels and neuropsychiatric symptoms in PKU are as follows. Firstly, there is an overreliance on studies with low participants, this is to be expected with a rare disease but in the future multicentre studies should be used to overcome this. Secondly, the literature does not represent the UK population as no studies have been completed here. In addition, the age of participants is generally young which does not represent the entire PKU population, as some studies have found a correlation

between age and neuropsychiatric symptoms in PKU patients, having a young study population may risk underestimating the burden of neuropsychiatric symptoms in PKU populations. Thirdly, the literature uses a wide range of different questionnaires and screening tools which may not be directly comparable. Finally, there is no accepted measure of Phe levels with studies using a range of methods (current, 6-month average, 2-year average) which may obscure the relationship between phenylalanine levels and neuropsychiatric symptoms.

Weighing of evidence

As the randomised control trial is the strongest form of evidence available in this literature review, there is strong support for a link between Phe levels and an increased prevalence neuropsychiatric symptoms. However, further work needs to be done to consider the impact of a range of confounding factors (socio-economic status, age, gender and other biomarkers such as tyrosine and tryptophan).

Method of audit

In 2017, a systematic audit was undertaken using the clinical database maintained by the Mark Holland Metabolic Unit at Salford Royal Hospital. The database contained 244 patients with PKU, 24 patients had no recorded Phe levels in the last 2 years so were excluded from the audit.

The 2-year average Phe level was used as the measure of Phe control. This was calculated using the mean Phe level of each patient using all measurements recorded on the clinic letters in the previous 2 years. Mental health diagnoses were recorded by using a search function for “Depression”, “Anxiety”, “Low Mood”, “Mood swings”. If the terms were used by a clinician in a list of diagnoses or a problems list this was recorded as a positive result. Patient age, gender and pregnancy status were also recorded. Odds ratios (with 95% confidence intervals), were calculated to establish the association between Phe level >600mg/L and mental health diagnoses.

Following the results of this audit and discussion of the limitations, two following re-audits were undertaken in 2018 and 2019. In 2018, the audit cycle was repeated by re-auditing the same group of patients 1 year later. This audit used a 1 and 3 year average Phe level and also used additional search terms such as “migraine”, “Headache”, “Tired/Tiredness” and “Fatigue”.

In 2019, a Quality Improvement Personal Excellence Project (QPEP) was undertaken with the aim of assessing the quality improvement impact of the project, finishing the associated research paper and continuing to implement the recommendation of the audit. This involved engaging with health professionals and patients at the PKU health professionals day 2019 and PKU patients day 2019. As part of this Becks and HADS scores were used to provide a qualitative measure of mental health symptoms in the Mark Holland metabolic unit PKU population.

Results

Results included in the appendix

Discussion

1. Identify if mental health conditions are a significant health issue in the Mark Holland metabolic unit PKU population

The 2017 audit found a significant burden of mental health conditions in this population.
• Depression (14%)
• Anxiety (19%)
• Low mood (15%)
• Mood swings (10%)

2018/2019 audit found
• BECKS 54.2% depression
• HADS 14.8% depression
• HADS 37% Anxiety

2. Continue an Audit loop and identify how it can be repeated and improved

The audit loop was repeated in 2018, the audit was then followed up with a quality improvement project in 2019.

3. Evaluate the effectiveness of the current database system for the storage of patient data

The database in 2017 was inadequate for several reasons,
I. 80+ patients had no information other than ID numbers.
II. Many patients were duplicated
III. 24 patients were found to have no recorded Phe levels
IV. There was no mechanism for calculating average Phe meaning this had to be manually calculated taking considerable time and increasing the risk of error
In 2018
I. 18/264 patients had no recorded Phe levels - a slight improvement
II. No other information about the database was provided by the 2018 team, therefore, it is not possible to comment on other improvements in the database

4. Identify areas of opportunity and barriers to future research

The 2017 audit identified several future opportunities for research
I. Meetings were held with a statistician who recommended co-ordinating with other PKU centres
II. It was identified that diabetic patients could be a useful control for future studies as they have a similar burden related to diet.
III. A prospective study was recommended by making monitoring with HAD/BECKS scores routine in PKU clinics.

In 2019, further opportunities were identified
I. Working with the metabolic team mental health nurse to record HADS/BECKS in the clinic, combining this information with blood spot recorded Phe levels to have a more contemporaneous recording of mood and Phe

5. Assess the frequency of monitoring of Phe levels in comparison to NSPKU guidelines (monthly for non-pregnant patients)

							To have monthly testing patients would need to have 24 or greater tests in 2 years. In 2017, only 11 patients out of 202 patients with Phe levels had 24 or more tests, therefore 5.45% of patients had adequate monitoring according to the NSPKU guidelines. This will not include patients who have recorded Phe levels which are not included in their notes. In the 2018 audit, 4 out of 241 patients with recorded Phe levels had 24 or more tests recorded. This suggests that the number of patients receiving monthly Phe level testing has reduced over the last year. This may suggest that testing frequency has reduced or that patients have become less engaged with the service. More information gathering is needed to address the root cause of this, it may be that the current arrangement of clinics does not allow for monthly Phe testing or that the database is not accurately recording the number of Phe tests being undertaken. It would also be crucial to understand the patient perspective, do they want monthly Phe testing and is it feasible within the current clinic system? In pregnant patients, the mean number of tests over the last 2 years was 17. It was not possible to compare to the guidelines as the timing of pregnancy was not included in the database. 6. Assess the compliance with European guidelines relating to recommended adult Phe levels In 2017, 49 of 202 patients had a 2-year average Phe of below 600 µmol/L. Therefore 24.6% of the non-pregnant patients were adhering to the NSPKU European Guidelines. In 2018, 38 of 213 patients had a 2-year average Phe of below 600 µmol/L. Therefore 17.84% of non-pregnant patients were adhering to the NSPKU guidelines. Further information should be gathered on the cause of this decrease in patients adhering to control guidelines. Patient perspective should also be gathered to better understand the barriers patients face in controlling Phe levels within the guideline range. Pregnant: in Pregnant patients, the target is 120–360 µmol/L. In 2017, 9 of 17 pregnant patients had a 2 year average Phe level of <360. Therefore 52.94% were adhering to NSPKU European guidelines. However, as the period of trying to conceive and pregnancy itself may take anywhere for 10 months - >2 years the 2-year average Phe might not capture the adherence to pregnancy control accurately. Patients may have come off the diet after pregnancy, increasing their Phe level which would increase their 2 years average Phe. In 2018, 16 of 28 patients had a 2 year average Phe of <360. Therefore 57.14% of patients were adhering to NSPKU guidelines. Despite the previously discussed limitations of this measurement of control it is positive to see adherence in pregnancy improve. 7. look for evidence to support or dispute the NSPKU European		

guidelines – “Grade of recommendation: D In treated patients with PKU aged 12 years or older, the target phenylalanine concentrations should be 120–600 µmol/L.”(1)

All four mental health diagnoses had a odds ratio of > 1, therefore exposure to 2-year average Phe of greater than 600 µmol/L is associated with higher odds of each outcome (depression, anxiety, low mood, mood swings). Low mood has a 95% confidence interval of 1.0475 to 9.3114, as this does not overlap with 1 this suggests a statistically significant result. Depression, Anxiety and Mood swings both have overlapping 95% confidence intervals so the association of Phe >600 and increased prevalence of these conditions is not statistically significant.

The key measure of improvement

1. An increase in the number of patients under the 600ml/dl guidelines for Phe control

As discussed in section 6, there was a reduction in adherence in the non-pregnant population from 24.6% to 17.84%. There was an increase in adherence in the pregnant population from 52.94% to 57.14%.

Limitations

Limitations of initial 2017 audit

The limitations of the study are that due to its design it has no capacity to determine causality. In addition, there may be an issue of reverse causality due to timelines, this could occur if a depressed PKU patient tried to go back onto a low Phe diet. They would still be recorded as having a diagnosis of depression but would now have a lower Phe level. Therefore the association between Phe level and mental health diagnoses is uncertain as a diagnosis may not be contemporaneous to a Phe level.

Several variables were not controlled for and may be confounding including age, gender, socioeconomic circumstances and tyrosine/tryptophan levels. The study also relies on the accuracy of the patient record. There are many sources of error in electronic patient records including incorrect data entry and the introduction of incorrect diagnoses which are not later removed(12).

There may also be hidden time effects present, if there is seasonal variation in the prevalence of anxiety and depression then the 2-year sampling may not have equally sampled seasons with an increased incidence of anxiety or depression(13).

A final consideration is the role of diet in mental health symptoms. Other chronic diseases which involve restricted diet(diabetes) have an increased prevalence of mental health diagnoses(14). The PKU diet is significantly more restricting and patients may find it time-consuming and socially isolating(15). Being on a Phe restricted diet may itself be a source of stress and anxiety(16). This could increase the prevalence of anxiety in patients with low Phe and confound the result.

Limitations of 2018/2019 audit

HADS and BECKS scoring sheets were given to patients in clinics in 2018 and to patients at PKU day in 2019. As the groups were not randomised it is not clear if this is a representative group. The group may represent patients who are more motivated to engage with healthcare as they are attending patient days and clinics. It could be hypothesised that these results may underestimate depression as depressed patients may be more likely to not engage with healthcare professionals.

Strategy for change

From the 2017 audit 4 recommendations were made :
I. Repeat audit in 1 year
II. Becks depression score/HAD score – potentially fill in during wait for an appointment – especially in patients describing themselves as having "low mood"
III. Retest patients in the highest quartile – or consider why these patients are not engaged
IV. Look at database quality – 80+ patients do not have info other than ID number, some duplicates

1. A re-audit strategy was implemented – the re-audit took place in 2018 and assessed the recommendations as well as making further recommendations:
I. Re-audit in one years time
II. Larger implementation of surveys and formal recording of neuropsychiatric symptoms
III. Consider re-assessing how patients access the service to address the lack of Phe recordings in some patients and the absence of recordings in other patients
IV. Targets for the frequency of testing and Phenylalanine control should be reviewed, in particular patients in the highest quartile with the lowest frequency of testing

2. BECKS and HAD scores – 14 patients were given screening questionnaires by the 2018 team. In 2019, 16 patients had screening questionnaires recorded at the PKU patients day. The use of these screening questionnaires had not yet been made a routine part of PKU clinic, further discussion with stakeholders (Patients, Medical professionals) required to assess the feasibility and desirability of regular screening questionnaire use.

3. No formal retesting has taken place in this group.

4. Database quality has been improved with duplicate patients removed.

Effects of change

Patients have benefitted from an improved understanding of the mental health burden in the PKU population, this information was presented to patients during the PKU patients day and has been used to inform practice by recommending adherence to the NSPKU European guidelines. However, there has been no evidence so far of increased adherence to these guidelines and

						further studies are required to ascertain which barriers are preventing adherence in this population. Use of HADS/BECKs screening questionnaires will increase the sensitivity of mental health symptom detection in the future which may benefit patients. The employment of a mental health nurse by the department will support initiatives to treat patients with mental health symptoms. Conclusion The main aim of the audit was to identify if mental health conditions are a significant health issue in the Mark Holland metabolic unit PKU population. All 3 audits found a significant burden of mental health conditions in this population. The audit identified the limitations of the previous audit such as the issue of timelines not being contemporaneous which may lead to reverse causality. The audit responded to this limitation by suggesting a new approach using HADS and BECKS validated screening tools to monitor patient symptoms. Using this validated tools prevalence of depression was estimated at 14.8%-54.3% and prevalence of anxiety was estimated as 37%. The audit identified that 82% of non-pregnant patients are currently not adhering to the NSPKU guidelines of 600mmol/L Phe level. Evidence from the previous audit suggests that patients with >600mmol/L Phe were more likely to have a diagnosis of depression, anxiety or mood swings but these associations were not statistically significant. In addition, patients with Phe >600mmol/L are at significantly more risk of having a low mood diagnosis. This suggests that 196 patients are being exposed to high Phe levels which may be affecting their mental health. More support is needed to help these patients control their Phe level and to reduce the risks that poor control may pose. Recommendations 1. Despite increasing evidence supporting the benefits of adherence to NSPKU European guidelines the percentage of PKU patients following this guidance has reduced 6.8% – this requires further assessment and implementation of strategies to improve diet control such as low protein diet workshop days 2. Patients are still not receiving Phe testing at the frequency recommended in the NSPKU guidelines, further assessment is required to understand the cause of this 3. Re-audit cycle should be completed in 2020 to measure changes and progress towards key measures of improvement 4. The implementation of BECKS and HADS scores into routine practice should be discussed with stakeholders to identify opportunities and barriers. The addition of a mental health nurse to the metabolic team provides new opportunities for routine screening with HADS and BECKS 5. Further prospective research using screening questionnaires should be planned and included in the 2020 re-audit 6. In future treatments such as sapropterin dihydrochloride may become available in the UK, this may allow tighter control in some patients. This would allow further study into the benefit of very		

						tight Phe control <360mmol/L Reference list 1. van Spronsen FJ, van Wegberg AM, Ahring K, Bélanger-Quintana A, Blau N, Bosch AM, et al. Key European guidelines for the diagnosis and management of patients with phenylketonuria. Lancet Diabetes Endocrinol. 2017 Sep;5(9):743-756. Available from: doi: 10.1016/S2213-8587(16)30320-5. 2. Williams RA, Mamotte CD, Burnett JR. Phenylketonuria: an inborn error of phenylalanine metabolism. The Clinical Biochemist. 2008. Reviews, 29(1), 31–41.PubMed PMID: 18566668; PubMed Central PMCID: PMC2423317. 3. Sharman R, Sullivan K, Young R, McGill J, Depressive symptoms in adolescents with early and continuously treated phenylketonuria: Associations with phenylalanine and tyrosine levels. Gene. 2012 Aug 10;504(2):288-91. Available from: doi: 10.1016/j.gene.2012.05.007 4. Loeber JG. Neonatal screening in Europe; the situation in 2004. J Inherit Metab Dis. 2007 Aug;30(4):430-8. Epub 2007 Jul 6. 5. Ford S, O'Driscoll M, MacDonald A, Living with Phenylketonuria: Lessons from the PKU community. Molecular Genetics and Metabolism Reports. 2018 Dec; 17: 57–63. Published online 2018 Oct 18. Available from: doi: 10.1016/j.ymgmr.2018.10.002 6. Burton BK, Leviton L, Vespa H, Coon H, Longo N, Lundy BD, et al. A diversified approach for PKU treatment: routine screening yields high incidence of psychiatric distress in phenylketonuria clinics. Mol Genet Metab. 2013 Jan;108(1):8-12. Available from: doi: 10.1016/j.ymgme.2012.11.003. 7. Bilder DA, Burton BK, Coon H, Leviton L, Ashworth J, Lundy BD, et al. Psychiatric symptoms in adults with phenylketonuria. Mol Genet Metab. 2013 Mar;108(3):155-60. Available from: doi: 10.1016/j.ymgme.2012.12.006. 8. Brumm VL, Azen C, Moats RA, Stern AM, Broomand C, Nelson MD, Koch R. Neuropsychological outcome of subjects participating in the PKU adult collaborative study: a preliminary review. J Inherit Metab Dis. 2004;27(5):549-66. 9. Ris MD, Weber AM, Hunt MM, Berry HK, Williams SE, Leslie N.		

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Appendix – Raw audit data Quality improvement report using HADS, BECKS and retrospective audit to monitor mental health symptoms for PKU in a large single UK centre

Results

Descriptive results for retrospective audit

Age
Mean age was 35.9. The range of ages was 53 (18-71).

Symptoms
Overall 31(14.1%) patients had a diagnosis of depression. 42(19.1%) patients had a diagnosis of anxiety. 32(14.5%) patients had a diagnosis of low mood and 22(10%) patients had a diagnosis of mood swings.

Phe control

The mean Phenylalanine level was 944.6. The standard deviation was 443.46. The range of Phenylalanine levels was 1841 (162-2003). 49 of 202 patients had a 2-year average Phe of below 600 µmol/L. 9 of 17 pregnant patients had a 2 year average Phe level of <360. Therefore 52.94% were adhering to NSPKU European guidelines.

Number of Phe readings

The mean number of Phe readings was 7.1. The range was 69 (1-70).

Odds ratios

Diagnosis/symptom Odds ratio 95% Confidence Interval Significance
Depression 2.9 1-8.9 P = 0.0500
Anxiety 2.2 0.93-5.35 P = 0.0704
Low mood 3.1 1.04 – 9.31 P = 0.0410
Mood swings 4.3 0.98-19.1 P = 0.0524

Figure 1- Table shows the odds ratio, 95%CL and Significance for each symptom in the 2017 audit. The difference is between patients with Phe above and below NSPKU guideline.

Prospective results

Descriptive results

During the 2018 re-audit, 14 patients had HAD and BECKS results recorded. In the 2019 re-audit, 16 patients had a HAD and BECKS recorded.

BECKS

The Depression Inventory is a validated self-reporting questionnaire. 24 patients completed a BECKS screening tool survey either in the clinic or during the PKU patient day. Importantly, 54.2% of all patients had a BECKS score indicating they had depression. Mean score was 16.8. The range was 50 (1-51). In comparison to other outpatient populations, a recent metanalysis of the prevalence of depressive symptoms in an outpatient population estimated a prevalence of 36% using BECKS. This metanalysis included UK studies but also studies from other populations so may underestimate the prevalence in the UK if there is a higher prevalence of depression in the UK. However, as a crude comparison, it shows the high burden of depression in the UK population. In future, better-matched control groups such as the Salford outpatient population or diabetic population could be used.

Severity of depression Number of patients
Minimal depression 11
Mild depression 4
Moderate depression 5
Severe depression 4

Figure 2 - Shows the number of patients with each severity of depression according to the BECKS results

Figure 3 - The prevalence of each severity of depression represented as a pie chart

HADS scores

Descriptive results

27 patients had a recorded Hospital Anxiety and Depression Score (HADS). The HADS score is a validated self-reporting questionnaire. Mean score for anxiety was 9.85. The range for anxiety was 13 (7-20). Mean score for depression was 5.85. The range for depression was 21 (0-21). Prevalence of anxiety (excluding borderline cases) was 37%. Prevalence of depression (excluding borderline cases) was 14.81%. No estimated prevalence of anxiety using H

						Answer continued... AD in the UK population with suitable accuracy could be found. Severity of depression Number of patients Normal 18 Borderline abnormal 5 Abnormal 4 Figure 4 – a table showing the number of patients with depression using HADS score Severity of anxiety Number of patients Normal 11 Borderline abnormal 6 Abnormal 10 Figure 5 – a table showing the number of patients with anxiety using HADS score		
113					Has all of the relevant evidence been taken into account?	Figure 6 – Prevalence of anxiety using HAD displayed as a pie chart Figure 7 - Prevalence of depression using HAD displayed as a pie chart	Yes	National Society for PKU as well as Salford Royal NHS Foundation Trust
114					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	The outcome of PKU of maternal PKU in the UK has not been consistently captured via a registry of offspring. This evidence is therefore incomplete.	Yes	National Society for PKU as well as Salford Royal NHS Foundation Trust
115					Are the recommendations sound and a suitable basis for guidance to the NHS?	Women of childbearing age / planning pregnancy are not offered saproterin prior to pregnancy and therefore do not have access to a further option for controlling phenylalanine levels before critical periods of embryonic development	Yes	National Society for PKU as well as Salford Royal NHS Foundation Trust

116					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	yes - this issues relating to early pregnancy as outlined above yes - there are adult PKU patients who have varying degrees of disability e.g. autism spectrum, mild cognitive impairment, language/cultural barriers which may render dietary management more challenging	Yes	National Society for PKU as well as Salford Royal NHS Foundation Trust
117				PKU in adults Clinic population data We have audited the phenylalanine control of our clinic population during the last 5 years and noted 75% of the non pregnant adult population had phenylalanine levels exceeding the European recommended guidelines of <600 micromol/l. Contemporaneous clinic data indicated that 75-80% PKU patients were on some form of dietary protein restriction with the addition of protein substitutes. Through our retrospective audit of case notes we found increased rates of low mood in association with phenylalanine control above 600 micromol/ l as well as a trend to increased rates of anxiety, depression and mood swings. Subsequent prospective surveys in our clinics using questionnaires used in routine clinical practice (BDI, HADS) showed increased rates of anxiety (HADS) and depression (BDI) and mood disturbance in PKU adults compares with an unselected series of other patient in our clinic with a range of other rare or undiagnosed metabolic conditions. Of those women who were had a pregnancy during the 2 years preceding the audit, only 53% were in the target range of < 360 micromol/ l for preconception and pregnancy; in 2018 the corresponding figure was 57%. Whilst the majority achieve satisfactory control during pregnancy there remains the risk of unplanned pregnancies in a population who may not otherwise adhere to the phenylalanine restriction required to prevent adverse foetal outcomes. Case examples from our own clinic We encounter many examples of serious suboptimal outcomes from our PKU clinic population. Many of these situations occurred at a time prior to referral into our services. I would like to share some examples of patients I have personally reviewed in clinic in the 8 weeks since the start of 2021. I have generalized these vignettes to help preserve the confidentiality of specific individuals. Female patients of childbearing age: 1. A young adult female patient newly referred to the service having been diagnosed outside the UK and lost to follow up since adolescence. Though she reported that her GP was aware of the PKU diagnosis, she acknowledged she could not bear to resume dietary restriction with protein substitutes. Her PKU was rediscovered when her newborn baby was under investigation for profound developmental delay and multiple congenital anomalies subsequently attributed to maternal PKU syndrome. This severely disabled child is under a dozen specialists and will need such care for the rest of his/ her life, a circumstance that was in all likelihood entirely preventable with optimal phenylalanine control. An alternative to strict dietary management would have potentially encouraged this mother to engage much sooner. 2. A female patient with a long and complex eating disorder history, which developed on a background of severe phenylalanine restriction during childhood wishes to become pregnant. On resuming the strict phenylalanine restricted diet she is experiencing intrusive thoughts heralding a relapse of her eating disorder. To our surprise, mutation testing suggests she may be responsive to saproterin, but it is only availability for pregnancy once diet alone has failed and certainly not during the preconception period. 3. Another pregnant patient is struggling to achieve phenylalanine control, partly due to ambivalent			Yes	National Society for PKU as well as Salford Royal NHS Foundation Trust

				clinic engagement on a background of suboptimal control in childhood and involvement of social services. She already has several other children affected by maternal PKU syndrome Male patients: 1. A young man ‘s parent contacts the clinic. He has misunderstood the clear instructions and advice about returning to diet and has cut out dietary protein but not understood the need to contact the clinic to advise his choice of protein substitutes. He chose to return to diet to see if this would help his ‘brain fog’ .We arranged a further appointment to give further education in a face to face format as well as check his nutritional status especially given his 2 month period of severe unsupplemented protein restriction. 2. Another young man has also requested a face to face consultation - he is struggling with the combined effects of lockdown especially during winter, his PKU and the significant anxiety he experiences and is worried about the impact on his work. 3. A young student has found it too difficult to organise ongoing supplies of his PKU protein substitutes during lockdown and university term time. He has continued his strict low protein diet and we have needed to bring him to face to face clinic for nutritional assessment and blood tests. Close follow up has been needed to prevent long term sequelae. These latter vignettes are recent examples from my own clinic but prominent in that they are very representative of the clinical scenarios we see in adults with PKU Though perceptions across UK may vary regarding the impact of PKU on adults, the propensity for PKU to compound pre-existing social disadvantage may partly account for these apparent differences. Broadening treatment options has potential to address some of these health inequalities would provide an opportunity to address some of these inequalities.			
118					Has all of the relevant evidence been taken into account?	Yes but there is further evidence refrred to below. Performance of laboratory tests used to measure blood phenylalanine for the monitoring of patients with phenylketonuria: Moat et al: J Inherit Metab Dis. 2020;43:179–188.	No	

119					Are the recommendations sound and a suitable basis for guidance to the NHS?	I wwould wish to agree with one of your expert comments. I myself practice as a specialist in IMD in Paediatrics. The criteria for starting are very liberal - 30% reduction in Phe level as measured over one month. The points, which I am sue have been raised are: 1. Do you just take one level or an average as a baseline prior to beginning the trail of thearapy? 2. If weekly samples for one month are to be used, isi t the final level or an average over the one month? 3. When is the blood sample taken, we use the morning sample - which generally predicts the highest value. Levels will vary according to when the blood is taken and when in relationship to meals. 4. Will plasma levels or finger-prick samples be used ? Plasma levels are very accurate but require formal venous samppling. Finger-prick samples can vary significantly from sample to sample. There may have been other issues your expert referred to but I would support the contention that further time and attention needs to be given to the definition of criteria for treatment. See - Performance of laboratory tests used to measure blood phenylalanine for the monitoring of patients with phenylketonuria: Moat et al: J Inherit Metab Dis. 2020;43:179–188.	No	
120					Has all of the relevant evidence been taken into account?	Sapropterin also brings improved clarity, increase in mood and behavior. It is also known to improve cognitive function and improve gastric issues experienced by people with PKU. Further consideration of these benefits would be preferable.	No	
121					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	I have concerns over removal of the treatment at 18yrs. The diet is for life not just childhood.	No	
122					Are the recommendations sound and a suitable basis for guidance to the NHS?	I have concerns over removal of the treatment at 18yrs. The diet is for life not just childhood. I have concerns about not allowing Consultants the flexibility to give the full dose of 20mg/kg per day.	No	
123					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	I have concerns over removal of the treatment at 18yrs. The diet is for life not just childhood. At 18 many PKU sufferer's would not be equipped with the skills to manage the diet as they have not had practice. At 18 many young adults lose parental support by moving out of home or onto university. In addition they will have been used to certain foods not medical foods and can't switch between them.	No	
124	recommendations	1 Recommendations	they are under 18	I have concerns over removal of the treatment at 18yrs. The brain doesn't stop growing and changing, it continues well into 80's and 90's. The diet is for life not just childhood. At 18 many PKU-er's would not be equipped with the skills to manage the diet as they have not had practice. At 18 many young			No	

				adults lose parental support. In addition they will have been used to certain foods and can't switch between them.				
125	recommendations	1 Recommendations	a dose of up to 10 mg/kg is used	I have concerns about not allowing Consultants the flexibility to give the full dose of 20mg/kg per day. Some patients don't respond at 10mg/kg per day dosage but would respond at 20mg/kg per day. This treatment would change their life.			No	
126	recommendations	1 Recommendations	how it affects quality of life	Sapropterin also brings improved clarity, increase in mood and behavior. It is also known to improve cognitive function and improve gastric issues experienced by people with PKU.			No	
127	recommendations	1 Recommendations	There is also no risk of irreversible brain damage in adults with PKU	Phe level fluctuations impair cognitive function and mood and behaviour			No	
128	recommendations	1 Recommendations	here is also no risk of irreversible brain damage in adults with PKU	The brain doesn't stop growing and changing, it continues well into 80's and 90's. The diet is for life not just childhood. At 18 many PKU-er's would not be equipped with the skills to manage the diet as they have not had practice. At 18 many young adults lose parental support. In addition they will have been used to certain foods and can't switch between them.			No	
129	recommendations	1 Recommendations	PKU who are pregnant or trying to conceive	It's really difficult to get used to certain food and can't switch between them.			No	
130	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	2,000 people	Statistically there will be around 6500 people in England suffering with PKU.			No	
131	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	brain development does not stop until around age 25.	Brain development continues into 80s and 90s, it doesn't stop at a particular age.			No	

132	committee-discussion	People with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet	This can take 2 to 3 times as long as normal and make managing the diet a dominant activity of daily life	I cannot leave my son with carers without lengthy training on the diet. I have had to reduce my hours at work to enable me to shop, prepare and care for my son and his special needs.			No	
133	committee-discussion	People with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet	oor taste and disagreeable smell	my son has to take his supplement in a special cup with a lid which reduces the smell for him. The supplements also affect his breath and his teeth detrimentally.			No	
134	committee-discussion	People with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet	texture	The grainy texture of my son's supplement has made him gag and vomit. When this happens he has to be sent home from childcare and not allowed to return for 48hrs (nursery's infection control proceedure). This means we have to take time off of work to care for him.			No	
135	committee-discussion	People with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet	digestive problems.	My son with PKU experiences stomach aches, gas, acid reflux from the diet and supplements. He frequently wakes with night terrors and wets the bed from the volume of liquid he is required to consume.			No	
136	committee-discussion	People with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet	difficulties accessing prescription	It can take me over a month to receive prescription foods as they are not 'in stock' items at the pharmacy.			No	

137	committee-discussion	People with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet	as some are considered luxury items.	My son was not allowed prescription chocolate for Easter as it was deemed a luxury item. I think this is unfair as he should be allowed the same as other children.			No	
138	proposed-date-for-review-of-guidance	5 Proposed date for review of guidance	eview by the guidance executive 3 years after publication of the guidance.	With Biomarin losing the patent on Kuvan in Jan '21 it is expected that generic brands will available shortly thus proving a competitive marketplace. I would prefer to see a review after one year to enable the cost to be reevaluated in light of the emergence of generic alternatives.			No	
139				This is a great move forward however to limit the access to the quantity of the drug is immoral. Some patients are in effect only part medicated. Consideration also needs to be given to the age limit of 18. Despite the evidence of impact on adults, each individual will be different. The human body develops at different rates and has different needs. The medication should be distributed based on medical needs of the individual.			No	
140	committee-discussion	Recommending sapropterin for certain groups of adults cannot be justified given the cost-effectiveness estimates	people with a learning disability, sensory impairment, or cognitive impairment	To not provide Sapropterin to adults with PKU will mean that those adults who are not able to follow a strict dietary regime, such as those with a learning disability and cognitive impairment, will be unfairly disadvantaged. For those adults who have learning disability and cognitive impairment due to their high PHe levels due to difficulties following a dietary regime, they will experience an additional barrier and inequality.			No	
141	committee-discussion	Recommending sapropterin for certain groups of adults cannot be justified given the cost-effectiveness estimates	people in social care settings	The NICE proposals do not take into account the importance of the impact of stopping Sapropterin for a young person turning 18 who is in care and Looked After by their Local Authority. This is because at this time the young person's care starts ends and they will move out of foster care etc to look after themselves with the additional burden of learning a new dietary management system.			No	

142	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	Phe levels	The Recommendations on the dietary management of phenylketonuria report of Medical Research Council Working Party on Phenylketonuria (1993) states that blood the levels for adults over the age of 20 years should be kept to below 700, highlighting the need for Sapropterin therapy to do so. So far the only option for this is diet and by the same token PKU patients should be offered Sapropterin therapy.			No	
143	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	adult	Previous research (MacLeod & Ney, 2010) shows that low-phe diet remains the cornerstone for lifelong treatment of PKU. In other words, the diet is required to be adhered to for life, not just for children and adolescents. In the same way, Sapropterin must be offered as part of the life-long therapy.			No	
144	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	high Phe levels are unlikely to affect IQ.	It is incorrect to assert that, after the age of 12, high Phe levels are unlikely to affect IQ. There is evidence in previous research that even early-treated patients with PKU obtain lower IQ scores compared to unaffected familial controls and unaffected nonfamilial controls (Crossley & Anderson, 2010).			No	

145	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	.	Given that the brain is not fully developed until at least around the age of 25, the argument that this treatment should only be offered up to the age of 18 due to the impact on the developing brain does not stand. The 18-25 age group will require the same treatment as the 0-18 age group.			No	
146	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	considered reversible	The term 'considered reversible' is an over-simplification of the life of an adult with PKU. Dietary management of PKU is a complex process requiring input and guidance from expert dieticians and consultants. Assuming that the adult with PKU understands the process of how to manage their diet, there are then other cognitive and psycho-social factors which would affect this reversal and the choice to go back 'on-diet'. In order to make such a significant life choice and then have successful management of dietary strategies, the patient with PKU would need to be able to plan ahead, make clear decisions, inhibit their desire for other foods and these processes all relate to the use of executive function which is proven to be adversely affected by high Phe levels thus making this process cognitively much more difficult than it would be for non PKU adults. Also, there are numerous psycho-social factors to managing diet when having experienced cognitive impairment due to high Phe; these can include adverse impact upon mental health (potentially reducing drive and motivation to make changes and maintain good dietary adherence). For adults who have experienced high Phe and the impact on their cognition, their chances of being able to then manage their diet effectively is impaired. It is not simply 'reversed'.			No	
147	committee-discussion	Long-term brain damage in children is an important aspect of PKU, but there is little evidence to estimate its effect on quality of life	little evidence available to estimate its effect on the quality of life of people with PKU	There is no shortage of peer-reviewed research evidence regarding the impact of acquired brain injury (ABI) on quality of life (QOL). High levels cause brain injury to the adult brain. There is clear evidence of people acquiring a brain injury experiencing reduced mental health and quality of life. Even a mild ABI can negatively affect a patient's perceived quality of life to a great extent. There is no evidence to suggest that this is not the case for PKU patients in the same way as it is evidenced for the general population.			No	
148	committee-discussion	Sapropterin has not been shown to be cost effective in adults with PKU	sapropterin is not a cost-effective use of NHS resources for adults with PKU	This cost factoring has not taken into account the psycho-social impact of the new protocol for treatment of PKU. There will be a cost impact for those adolescents who turn 18, having had the provision of Sapropterin and have had to follow few dietary restrictions, then on turning 18 have there Sapropterin stopped. This is because of the psychological factors of such a huge change in lifestyle at such a key age. It is highly likely that this group will find a greater level of difficulty in adhering to dietary restrictions in comparison with those who had to follow only a strict dietary regime in their children thus learning how to do this and finding psycho-social methods of managing their life to avoid situations where they would be more likely to lapse in their dietary control. If NICE provide Sapropterin for young people up to the age of 18 only, they are storing up potential problems for this group who will have additional barriers to dietary maintenance as adults. This is likely to result			No	

				in higher PHe levels, lower cognition, difficulties with executive function and a resulting impact on social-economic factors thus negating the potential cost saving.				
149				We as a family are very happy with this decision. It could make our daughters life better. She could finally try some chips or chocolate. Thank you from the bottom of my heart.			No	
150					Has all of the relevant evidence been taken into account?	I feel that kuvan should be available for all and this document will help us reach that.	No	
151					Has all of the relevant evidence been taken into account?	No. You have not taken into account the experience of those with PKU and their families. Evidence can be qualitative as well as quantitative.	No	
152					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	No, not at all. There are many contradictions in the guidance, for example you state that there is no risk of brain damage after 18, but then state that the brain continues developing until the age of 25. A plethora of research demonstrates that brain development not only continues to the age of 25, but well beyond (reference below). It would follow that brain damage could therefore occur at any age, and even if it looks different in adulthood, it may still be significant. It is reductionist to state that the adult with PKU's brain is not at risk of irreversible damage, not least because research has not been carried out in elderly PKU patients. Newborn screening was only introduced in the 1950's/1960's. Before this time, those with PKU have severe brain damage. My taxes go towards paying your wages and for this level of contradiction, staggering...	No	
153					Are the recommendations sound and a suitable basis for guidance to the NHS?	Absolutely not. The drug is used in over 50 countries, including in Romania and Syria. Are you serious that we cannot prescribe this to those over 18 in the UK?	No	
154					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	I'm amazed you have asked this question when you are actively and directly discriminating against women and those under 18. It sounds illegal.	No	

155	recommendations	1 Recommendations	they are under 18	Kuvan should be approved for all age groups. It should not be limited to just those under 18. This guidance underestimates the benefits of Kuvan treatment for adults with PKU. It says there is no risk of permanent brain damage after the age of 18, but this is directly contradicted by the statement that the brain continues to develop up until the age of 25. More recent evidence shows that brain development continues to develop well into old age. Many adults with PKU have very serious symptoms – such as depression, anxiety, brain fog and memory loss - caused by high phenylalanine levels. Protein allowance does not typically increase as patients get older and therefore dietary treatment and management only gets more difficult in adulthood. The NHS has also sine 1993 recognised and endorsed that dietary treatment is for life. PKU is not cured once a person turns 18. The draft guidance does not stipulate or consider the impact on a patient taking Kuvan in childhood and then having it withdrawn on their 18th birthday. These 18-year-olds are often at a crossroads in their lives at this point, for example going to university or leaving home. Managing phenylalanine levels with dietary treatment alone is very difficult, especially for teenagers. 18-year-olds accustomed to a relaxed diet through using Kuvan would not have the coping skills and tools to switch to an extremely restricted diet and would go on to suffer a whole host of issues and symptoms. This issue has been completely ignored in the guidance.			No	
156	recommendations	1 Recommendations	a dose of up to 10 mg/kg is used	Draft guidance says “a dose of up to 10 mg/kg is used”. This cap should not be in place. Clinicians should have the flexibility to prescribe the dosage according to individual patient needs and in line with the manufacturers authorisation which ranges from 5mg/kg to 20mg/kg. With this current guidance, there is a large risk that many patients would be classified as non-responders, when they in fact need the higher dose of 20mg/kg. This is the common practice in other countries. The costing against 10mg/kg is appropriate as that is likely to be the average dose, but clinicians need the flexibility to prescribe up to 20mg/kg where required. The decision to cap the dosage is purely a cost reason, not a clinical decision. All other countries don’t have this cap, so why is the UK recommending this?			No	
157					Has all of the relevant evidence been taken into account?	No, Evidence on the detrimental effect of high phenylalanine levels on the foetus has not been discussed/found/ nor considered in the cost analysis. The consultation proposal will affect mothers to be with PKU over 18yrs age. If we want to protect children, we should also protect the foetus that is to become a child. No, evidence for the brain developing up to the age of 25yrs has not been considered.	No	
158					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	The cost of High Phenylalanine levels on Mental Health Issues requiring: counselling, psychology, medication for anxiety/depression, time of health professionals, in a patient's adult life I has not been considered/calculated. I cannot see that the cost of supporting patients with learning disabilities has been considered. Following on from my comment above regarding the Pregnant mother with PKU: Damaging the foetus with maternal high phenylalanine blood levels will compromise their health and the cost of this should be considered: Brain damage causing the need for additional social care, disability living allowance and Health Professional support and thus the cost to the nhs.	No	

159					Are the recommendations sound and a suitable basis for guidance to the NHS?	I believe they are unethical: segregating children from adults. Allowing children the opportunity to have Sapropterin but taking it away from them at 18years of age when at that age the patient will have so much to learn: new job, university, independence, self-responsibility, living away from home, following an incredibly restricted diet - that will become even more restricted if Sapropterin is taken off of them.	No	
160					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	I am the Paediatric Dietitian for Inherited Metabolic Disease in South Wales. I have a current cohort of ~40 patients with PKU. Of this cohort I feel that there are a number of groups being discriminated against; Disability - 10% of this cohort, my medical team and I would consider to have learning difficulties. Once they are 18yrs of age they are unlikely to have the capacity to learn the additional restriction on diet required if they have to come off of Sapropterin at 18yrs of age. Disability - 50% of this cohort the metabolic team and I consider to be in poverty either due to a single parent, a single income family or low income. This won't change when they become 18yrs of age. Gender - 15% of this cohort are female and currently of child bearing age. Once they become 18yrs they are being discriminated against with regard to considering having children in a safe way where the phenylalanine levels need to be extremely low (<360ug/L) to have a child protected against the effects of phenylalanine in the circulating maternal blood. Coming off Sapropterin at 18yrs would make having a child in a safe manner much more difficult and much more stressful. Disadvantaged groups - 15% of my cohort are from the traveller communities which are believed to be disadvantaged due to their ethnic origin. Once they become 18yrs of age they will be doubly disadvantaged because they are no longer allowed to have Sapropterin.	No	
161	recommendations	1 Recommendations		Restricting treatment to children alone is a dangerous and misinformed proposal which creates a cliff edge for young adults reaching 18. It is unreasonable and unrealistic to assume that those reaching 18 will successfully be able to commence a protein-restricted diet for the first time and therefore you create two scenarios in which either a) PKU patients fail to ever follow their diet at all and then suffer the consequencies of toxic build up of PHE or b) they are subjected to countless emotional and psychological battles while struggling to exercise the diet properly. PKU is a lifelong battle and in the case of those successfully following a diet it more often than not relies on the complete mystery of the unknown. For those, like myself, who voluntarily came off diet for 10 years and then returned again at 24, it is now a lifelong battle to try and return to what I did as a child in the knowledge of how "the other side live". It is a challenging and difficult task filled with guilt, shame, and cognitive consequences when I fail to "stay on the wagon". Asking a young adult to suddenly cut out 95% of their diet and restrict protein for the rest of their life, in my view is cruel and I wouldn't wish that upon anyone. It's hard enough trying to exercise protein best practices when I know what good dietary control looks like and when I've already had 14 years of childhood living with restrictions, so it is ridiculous to assume that exercising this lifestyle without a lifetime of experience and at such a crucial point is even remotely possible or acceptable. Please reconsider your stance on this. I would personally not allow any child of mine with PKU to engage with this drug and instead opt keep them on a low-pro diet instead for all the reasons aforementioned. Restricting access in this way postpones many issues and exacerbates many others.			No	

162					Are the recommendations sound and a suitable basis for guidance to the NHS?	No they are not, since the recommendation encourages PKU patients to stop treating their condition as young adults, which those of us who have been treated for this condition until now have been advised is dangerous and not recommended. I strongly believe this will result in lower quality of life for PKU patients in future.	No	
163					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	Clearly there is a some discrimination based on age. since older patients may not access the treatment despite potentially being able to benefit from it. This decision seems to have been based on cost rather than the best interests of PKU patients.	No	
164				I am a 35 year old woman who has been treated for PKU since shortly after birth. My doctor in [redacted] advised me, years ago, that it was unlikely I would respond to Kuvan so I have never pinned much hope on this treatment for myself, but as someone with experience of this condition I felt compelled to respond. I can only assume this draft guidance was written by someone who does not understand PKU. Treatment with Kuvan until age 18 only seems likely to result in poorer outcomes for PKU patients than the current "diet for life" treatment. I manage very well on my diet due to a lifetime of practice but I can't see how it would be possible to form the good habits and discipline to do it successfully starting at age 18, after years of a more relaxed diet. Even for someone with good dietary control like me, the diet becomes more challenging in adulthood as you begin to manage it alone with less parental help and have new considerations to take into account, such as avoiding social embarrassment in situations involving food, trying to explain the seriousness of the condition to people who haven't heard of it and don't understand/ believe you, and simply being hungry and needing to cook for yourself. I can't imagine most teenagers will bother adhering to the diet at all, especially without having developed the coping skills earlier in life. Frankly, I think not providing Kuvan to PKU patients at all is preferable as patients can achieve good outcomes through the dietary treatment, but only if they are taught to do it from an early age. Treating PKU with Kuvan only until 18 just seems cruel to me. I was also concerned by the statement in the guidance that there is no risk of irreversible brain damage to adults with PKU, as this contradicts everything I have ever been told about the condition by the neurologists that have treated me in [redacted] and [redacted]. My doctors always indicated that the risks to the brain for adults are unknown. This guidance suggests to me that I am wasting my time continuing to treat my PKU in adulthood since there is no risk. While I'm sure that my doctors are advising me correctly and that the guidance is wrong, I fear that this will encourage future PKU patients to take their condition less seriously in adulthood which seems dangerous to me. I strongly urge NICE to reconsider this recommendation which, from the perspective of a well-treated PKU patient, seems highly likely to result in poorer outcomes and lower quality of life for future PKU sufferers.			No	
165				This drug should be available for over 18 year olds. It’s life changing if individuals cannot continue with a drug that will give them a degree of quality of life			No	

166				As Dietitians working with and supporting adults with PKU, we have seen first-hand the challenges that adults with PKU experience. Suboptimal phenylalanine control in adulthood has been shown to lead to attention deficit, mood disturbance and impaired executive function. Current European Consensus guidelines recommend lifelong treatment for the management of PKU and therefore adults with PKU are encouraged to continue a restricted diet throughout their lives. The PKU diet is incredibly demanding and many find it challenging to adhere to. A young adult with PKU, in addition to the challenge of the restricted diet, also has to face the regular challenges faced by their peers at 18 years old. Examples include trying to increase their independence, moving out of home, going to university or starting their first jobs. These challenges are magnified considering their restricted diet which they will be beginning to manage themselves, which therefore makes adhering to their PKU diet even more difficult. Stopping Saptopterin at this time would amplify these difficulties further likely decreasing adherence resulting in a rise in phenylalanine levels – further exacerbating these challenges and the individual's ability to cope with them. Furthermore, high phenylalanine levels can significantly impact on an individual's ability to actively participate and succeed in further studies or when embarking on their career. This in turn can negatively impact on their future career opportunities, contribution to society, and quality of life. As no treatment for PKU should stop at the age of 18 years, neither should Saptopterin for those who are BH4 responsive. The impact of loss of phenylalanine control with stopping Saptopterin in addition to the increased demands of then needing to follow a strict phenylalanine diet, is putting young adults at risk neurological and behavioural issues, and reduced quality of life. In addition to these concerns, availability of Saptopterin throughout the lifespan would enable women of childbearing age to be established on a dietary regime that incorporates Saptopterin prior to conception, rather than taking a reactive approach to high levels as is current practice. This would decrease the risk of high phenylalanine levels to the foetus (congenital heart disease 12%; intellectual disability 92%; microcephaly 73%; birth weight <2500g 40% and spontaneous abortion 24%) and help to decrease the levels of stress associated with this for the mother. We would be grateful if NICE could take into consideration the impact that discontinuing Saptopterin at the age of 18 years would have on our adults and future generations living with PKU.			Yes	Guy's and St Thomas' Adult Inherited Metabolic Diseases team
167				1. Draft guidance says "a dose of up to 10 mg/kg is used". This cap should not be in place. Clinicians should have the flexibility to prescribe the dosage according to individual patient needs and in line with the manufacturers authorisation which ranges from 5mg/kg to 20mg/kg. With this current guidance, there is a large risk that many patients would be classified as non-responders, when they in fact need the higher dose of 20mg/kg. This is the common practice in other countries. The costing against 10mg/kg is appropriate as that is likely to be the average dose, but clinicians need the flexibility to prescribe up to 20mg/kg where required. 2. Kuvan should be approved for all age groups. It should not be limited to just those under 18. This guidance underestimates the benefits of Kuvan treatment for adults with PKU. It says there is no risk of permanent brain damage after the age of 18, but this is directly contradicted by the statement that the brain continues to develop up until the age of 25. More recent evidence shows that brain development continues to develop well into old age. Many adults with PKU have very serious symptoms – such as depression, anxiety, brain fog and memory loss - caused by high phenylalanine levels. Protein allowance does not typically increase as patients get older and therefore dietary treatment and management only gets more difficult in adulthood. The NHS has also since 1993 recognised and endorsed that dietary treatment is for life. PKU is not cured once a person turns 18. 3. The draft guidance does not stipulate or consider the impact on a patient taking Kuvan in childhood and then having it withdrawn on their 18th birthday. These 18-year-olds are often at a crossroads in their lives at this point, for example going to university or leaving home. Managing phenylalanine levels with dietary treatment alone is very difficult, especially for teenagers. 18-year-olds accustomed to a relaxed diet through using Kuvan would not have the coping skills and tools to switch to an extremely restricted diet and would go on to suffer a whole host of issues and symptoms. This issue has been completely ignored in the guidance.			No	

168				I've read through this document and was initially pleased to see this treatment being introduced in the UK however I am concerned that the usage is quite restrictive. The dosage is capped at half of what would be an efficient treatment for many, and with it only being available until the age of 18 , it will not provide care for the remainder of someones life, despite the symptoms of PKU not stopping at 18 and having to adjust to an extremely restrictive diet as a teenager would be quite difficult and dangerous if you've recently embarked upon independent living for the first time and could be a quite tramatic too. Whilst It's good to see that this treatment may be available for the first time, its options for usage need to be broadened to include the full recommended dose as per other countries, as well as being available for people above the age of 18 for whom its will make a marked difference to the management of their condition			No	
169				I would like to comment as follows: 1. Draft guidance says "a dose of up to 10 mg/kg is used". This cap should not be in place. Clinicians should have the flexibility to prescribe the dosage according to individual patient needs and in line with the manufacturers authorisation which ranges from 5mg/kg to 20mg/kg. With this current guidance, there is a large risk that many patients would be classified as non-responders, when they in fact need the higher dose of 20mg/kg. This is the common practice in other countries. The costing against 10mg/kg is appropriate as that is likely to be the average dose, but clinicians need the flexibility to prescribe up to 20mg/kg where required. 2. Kuvan should be approved for all age groups. It should not be limited to just those under 18. This guidance underestimates the benefits of Kuvan treatment for adults with PKU. It says there is no risk of permanent brain damage after the age of 18, but this is directly contradicted by the statement that the brain continues to develop up until the age of 25. More recent evidence shows that brain development continues to develop well into old age. Many adults with PKU have very serious symptoms – such as depression, anxiety, brain fog and memory loss - caused by high phenylalanine levels. Protein allowance does not typically increase as patients get older and therefore dietary treatment and management only gets more difficult in adulthood. The NHS has also since 1993 recognised and endorsed that dietary treatment is for life. PKU is not cured once a person turns 18. 3. The draft guidance does not stipulate or consider the impact on a patient taking Kuvan in childhood and then having it withdrawn on their 18th birthday. These 18-year-olds are often at a crossroads in their lives at this point, for example going to university or leaving home. Managing phenylalanine levels with dietary treatment alone is very difficult, especially for teenagers. 18-year-olds accustomed to a relaxed diet through using Kuvan would not have the coping skills and tools to switch to an extremely restricted diet and would go on to suffer a whole host of issues and symptoms. This issue has been completely ignored in the guidance.			No	
170	committee-discussion	Treatment pathway		Children with a restricted PKU diet are so very limited with their choice of foods. They cannot enjoy the diet their peers enjoy, attend parties without prior arrangements being made. My friend's son has PKU and I know the struggles she has ensuring that he eats food he enjoys.			No	
171					Has all of the relevant evidence been taken into account?	I have read this document and I feel that you have barely taken into account the lived experiences of those with PKU and their carers. Evidence can be qualitative as well as quantitative. Many people with PKU were advised by the NHS to come off the diet in their childhood and have paid massive consequences. The NHS has let these people down before and you are on course to repeat history.	No	
172					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	I am staggered to hear a drug that is routinely used in Syria is not deemed a cost effective option in one of the most developed societies in the world. It is not cost effective because you will be giving children half a dose and wasting it because it will show they don't respond.	No	
173					Are the recommendations sound and a suitable basis for guidance to the NHS?	Absolutely not. This is lip service. Do the moral an right thing and unleash the potential for those with PKU and their parents.	No	

174					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	Incredible question when you are discriminating directly on age!!! and Maternity!	No	
175				My cousin is a parent to a child with PKU. I see and hear of the struggles they have on a daily basis with the management of the dietary treatment, and fear and have worry for their future. I am shocked you are recommending to withdraw treatment to my cousins child when he turns 18. He will go from a relaxed of say 15-20g a day, much more in line with a natural vegan or vegetarian diet, back to 5g of protein a day where he will have to learn from scratch the knowledge and tools to cope with this dietary treatment, for example how to order prescription foods. I fear his life will be turned upside down at this point when he is stripped of this drug, at a time when he would be sitting exams, applying to university and potentially leaving home. I have read the symptoms and heard the stories of people coming off the PKU diet. It is not pretty. I am scared for my cousins child based on your recommendations, it is short-sighted and weak in nature. The consultation gives no proof that you understand the daily life of someone living with this condition. Research from McDonald in 2016 shows for a carer/parent of someone with PKU, it takes up 19 hours per week. From tasks such as forcing the foul tasting supplement down children, baking all their food from scratch and endless calls to GPs for prescription food - you do not take this into account and you are not listening to the experiences of those with PKU as evidence, purely going off the limited research available, limited because it is a rare condition. I was also staggered to hear you are recommending capping the dosage at HALF of what the manufacturer recommends and is commonly prescribed in other countries. If I had a headache, I would not say paracetamol is ineffective if I took 1 tablet, I would take 2 tablets. With this guidance, you are setting children up to fail by saying Kuvan is ineffective, when in fact it is because you are giving them half a dose. Doctors need to have the flexibility to prescribe within the recommended range. Some children will need the full dose of 20mg/kg for the drug to have an effect. Some will need 10 or 5mg. It is not for NICE to cap that PURELY because of cost reasons. If you think this treatment works for children, which you do by giving your recommendation, then don't do a half arsed job, let doctors treat patients and not have their hands tied by corners being cut.			No	
176	recommendations	1 Recommendations		Although I'm very happy to see some desperately needed development on treatment for PKU, and the ability to use Kuvan as a method for that, I am disappointed by a few of the limitations set in place, and medical contradictions raised by this new approval. Firstly, a capped dosage of 10mg/kg may not be adequate for many, effectively placing them into the non-responders group incorrectly (eventually ceasing treatment). This could put many at permanent, lifelong, daily risk. Clinicians should have the flexibility to dose as necessary, per patient, as is the common practice in many other countries already widely using Kuvan as a form of dietary management for PKU sufferers. Allowing a wide range from 5-20mg/kg (manufacturers approved dosages) would allow for better, safer management on a personal level. Secondly, stopping treatment at 18 years old due to the belief that brain development would not be affected after this age, comes in direct contradiction to medical studies that have found brain development continues well into later life, and very actively up until the age of 25. PKU is a lifelong issue, it does not disappear with age. Adults should also be given the ability to manage their diet effectively to help positively impact their quality of life. Side effects of living with this condition are found to be depression, anxiety and memory loss, among others. Additionally, at 18 years of age, many pivotal aspects of life are changing, for example leaving home to got to university, which could introduce an extra level of complexity and daily risk, managing a newly restrictive diet after having the treatment ceased. I hope that these and the other points raised by so many people affected by PKU, will allow for reconsideration and amendment of the ruling around the use of the drug as a dietary management solution.			No	

177					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	The guidance on stopping at 18 years of age is extremely difficult because: - 18 years of age is a very complicated time for a young person with a chronic health condition due to the transition of their care to adult services. This is also an important time for social interaction, changes in independence and the exposure to alcohol. - The commencement of a medication that will be stopped is a very difficult decision for a parent to make. A child of 15 years maybe eligible but this puts great strain on the parents to make a decision to commence medication that will have to be stopped. - The effect of stopping medication that has improved a persons well being and improved their life will have detrimental effect on the individuals psychological well being.	No	
178				My Granddaughter who is 15 weeks old today was born with PKU,I'm grateful for the fact that she will have the opportunity to be given the Kuvan trial and hope with all my heart that she responds well to the trial . However find it hard to believe that on turning 18 a critical time in their lives these unfortunate people are denied the drug which enables them to lead a more normal life we live in the 5th wealthiest country on Earth and I don't think that funding this drug for approximately 6000 people this is roughly the amount of people with this disease would break the bank			No	
179					Has all of the relevant evidence been taken into account?	Yes but adults need to be given this drug as well. I understand that it will cost more but how would you feel if you were told you could no longer have something because it would now make you ill? Yes it doesn't cause brain damage in adults but it still greatly effects their mental health and stops them living an as normal as we can life. It's very unfair. It's awful knowing my baby can only have this until 18 - part of me doesn't want to put him on it if he just have them reduced again! This needs sorting and giving to adults, the poor people have already been denied it for years!	No	
180					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	No, everyone needs this. As in my previous answer it may not cause damage to the brain of adults but it effects mood etc and if they need mental health support they will then be seen as a 'drain' on the NHS. Everyone, from 0 to 100, who responds needs to be given this medication	No	
181					Are the recommendations sound and a suitable basis for guidance to the NHS?	No, everyone should be given it. My reasons are stated above	No	
182					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	You are being age discriminative because of not giving it to over 18s. Its appalling and I am sure i am not the only one thinking this. If you are a responder you should be given it. That simple	No	

183	recommendations	1 Recommendations		So what about the children who get a significant increase in exchanges? They are just expected to drop back down to their current levels? My son currently is on 11 exchanges so it is likely he will respond and I have read this drug could triple his number of exchanges. So at 18 he has to drop back down from 33 to 11? When he's been able to have all these things? Being on diet alone can cause a number of mental issues in adults as you have stated in the next section, these issues will be seen as a 'drain' on the NHS, everyone who responds should be given the drug. Fine children first but then adults! PKU doesn't just disappear at 18! Very disappointed			No	
184	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults		So if you acknowledge that the brain is still growing until 25 why is the drug being stopped at 18?			No	
185	committee-discussion	There is a need for a treatment that can reduce PKU symptoms and give people with PKU and their carers peace of mind about blood Phe levels		Then surely all these points you should give it to everyone?			No	
186	committee-discussion	Sapropterin has not been shown to be cost effective in adults with PKU		Quality of life will go down at a very important time in their life! As they begin university and have to explain their condition to lots of new people who won't understand and will be pressured to try things they can no longer have due to no longer taking the drug, again this will effect mood etc and seen as a 'drain' on the NHS			No	

187	committee-discussion	Sapropterin is recommended at a dose of up to 10 mg/kg in children under 18 with PKU for treating HPA that has been shown to respond to sapropterin		What if they need more than this? Are you saying they can't have it?			No	
188	committee-discussion	Sapropterin is not recommended in adults with PKU for treating HPA that has been shown to respond to sapropterin		Well they should, it's time we thought of people and not just the economy!			No	
189				My daughter is 8 years old and lives with PKU, she finds this very hard as she can only eat certain foods, she is a fussy eater and won't eat the prescription foods which makes this more difficult and we have a daily battle as she wants to eat more normal foods and gets very upset as she can only eat small amounts of foods with protein in it and gets very angry when she asks for more and we have to say NO, as parents we find this very hard and upsetting also to be refusing our daughter foods that she loves, this medicine would make a huge difference to her life and also ours, she just wants to eat the same foods as her friends and doesn't want to feel left out or different, and be limited to what foods she can eat			No	
190					Has all of the relevant evidence been taken into account?	No, the committee has dismissed certain models and evidence , particularly in determining and qualifying the quality of life.	No	
191					Are the recommendations sound and a suitable basis for guidance to the NHS?	No, the recommendations are directly discriminatory on the basis of age (in denying treatment at the age of 18 despite there being no improvement in symptoms at this age, and despite evidence that the developing brain is most at risk from irreversible damage up to the age of 25) and on the basis of gender, given that women of child-bearing age will be on a more onerous and expensive diet than their peers.	No	
192					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	As mentioned the decision is discriminatory on the basis of age (no improvement in symptoms, but refusal to fund treatment at the age of 18), and on the basis of pregnancy and maternity as women will be at greater risk of having a child with irreversible brain damage and will also be placed on a much more expensive and onerous diet before becoming pregnant.	No	

193	recommendations	1 Recommendations	they are under 18	Nothing changes in the symptoms of PKU from the age of 17 to 18, so ceasing treatment at that age is discriminatory on the basis of age.			No	
194	recommendations	1 Recommendations	in babies and children	And adults up to the age of 25 (the brain is susceptible to irreversible damage all the while it is still developing)			No	
195	recommendations	1 Recommendations	no extra increase in quality of life for adults to offset these costs	This is factually incorrect, and every adult sufferer of PKU will explain to you that quality of life is severely affected by the diet, which is so incredibly restrictive as to be impossible to follow. It is not possible to stay 'on diet' and work full time due to the extremely onerous nature of following the diet. It is not possible to work full time if the diet is not followed due to the effects of uncontrolled blood phe levels. It can be impossible to travel, due to the extraordinary quantities of supplements that need to be carried if going abroad. It can be impossible to go abroad, due to the different food labelling in other countries, not to mention the language barrier. These are just some small examples of how quality of life is absolutely diminished for people living with PKU.			No	
196	recommendations	1 Recommendations	not enough evidence on how sapropterin might be used to prevent harm to the unborn child in women with PKU who are pregnant or trying to conceive. So, sapropterin is not recommended for adults.	Then more evidence needs to be sought before this decision is rubber stamped. It is widely medically acknowledged that harm to an unborn child is highly likely where a woman is unable to control her blood phe levels effectively. The current guidance seeks to put a solution in place only after a woman has shown she cannot control her blood phe levels after she is pregnant, thus creating serious harm to the unborn child. You have also discounted the duration of a woman's life she might spend trying to conceive. For many women this could be months, or even years. Therefore your decision not to even investigate the impact on woman pre- and during pregnancy is discriminatory against women of child-bearing age with PKU, who will be under an even more restricted diet for an even longer period of her life than a male sufferer of PKU.			No	
197	information-about-sapropterin	Marketing authorisation indication	who have been shown to be responsive to such treatment	Does your decision take into consideration the low number of people (even within the already low numbers of people with PKU) who will actually be able to take Kuvan, and therefore recognise that the real cost of Kuvan is not a simple multiplication of how many people have PKU?			No	
198	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	the developing brain	The brain is still developing up to the age of 25			No	

199	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	reversible neurological changes i	Only reversible by returning to an extremely burdensome and complex diet, which an adult suffering from neurological changes will have even greater difficulty following than the average person.			No	
200	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	can cause irreversible damage during brain development	the brain is developing up to the age of 25			No	
201	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25	Then there is no justification for stopping treatment at the age of 18			No	

202	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	short-term symptoms,	The duration of the symptoms depends entirely on the individual's ability to get back on an extremely complex and restricted diet, which will be made extremely difficult due to the common symptoms of uncontrolled blood phe levels.			No	
203	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	The committee concluded that PKU is associated with high blood Phe levels that can lead to irreversible damage to the developing brain.	As discussed, the brain is developing up to the age of 25, therefore there is no justification for stopping treatment at the age of 18			No	

			The experts explained that Phe levels should be kept low throughout the whole pregnancy. Dietary measures should ideally be started before conception to avoid congenital effects, but at least at the earliest possible opportunity to avoid harmful effects on the unborn child. However, the committee noted that about half of pregnancies are unplanned. As a result, women may be fearful of becoming pregnant, or worried that they may not be able to cope with the protein-restricted diet during pregnancy. One patient expert highlighted that there is an NHS policy in place for providing sapropterin for pregnant women with PKU. The NHS England commissioning expert and the patient expert indicated that the NHS policy only covers women with PKU who are already pregnant who are unable to establish Phe levels that are not harmful to the unborn child (100 to 300 micromoles per litre) on a protein-restricted diet. Only then can they be tested for a response to sapropterin. The experts stated this delay in starting sapropterin can result in the unborn baby being exposed to high Phe levels in the critical phase of early pregnancy before sapropterin is given. Clinical experts confirmed that the outcomes for pregnant women with PKU are better in the UK than other countries such as the US. But they are not ideal, and the current NHS policy is not optimal. The committee concluded that high						
204	committee-discussion	High blood Phe levels in pregnancy can have harmful effects on the unborn child		Did the committee take into consideration the duration of pre-conception and by how much this can vary? Has the committee been presented with a sample diet of a woman on the pre-con diet? Can anyone on the committee truly accept that to be on such a diet for a minimum of one year (supposing 3 months pre-conception and 9 months full-term pregnancy) is reasonable and unlikely to affect quality of life? And have you considered women with PKU who already have children who become pregnant? Your discriminatory decision will have a direct impact on whether a woman with PKU can cope with the diet well enough to a) have children or b) grow her family. By reaching this decision you are severely limiting a woman with PKU's life choices.				No	

			blood Phe levels in pregnancy can have harmful effects on the unborn child. Early control of Phe levels, ideally before conception, would reduce the risks.						
205	committee-discussion	3 Committee discussion	The ERG produced 2 scenarios with 0% and 71.2% reductions. The committee concluded that the cost savings related to a reduction in protein-restricted diet are uncertain. Comment on section: The costs of long-term brain damage and damage to the unborn child in pregnancy may be substantial, but these have not been modelled	What threshold wold the ERG / committee consider is cost effective?			No		
206	committee-discussion	The only treatment option available for people with PKU is a self-managed protein-restricted diet	The committee concluded that the only treatment option available for people with PKU is a self-managed protein-restricted diet.	Does the committee understand what a protein-restricted diet entails? Has anyone on the committee role-played going to a restaurant as someone with PKU? Or buying lunch as a person on a protein-restricted diet? Or travelling abroad as someone on a protein-restricted diet?			No		

207	committee-discussion	People with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet	The time-consuming nature of food shopping and meal preparation. Also, the wide range of skills needed to understand food labels, calculate precisely, and weigh the amount of Phe in different foods that can be eaten in each meal, and prepare and cook meals regularly. This can take 2 to 3 times as long as normal and make managing the diet a dominant activity of daily life.	As a parent I am unable to work full-time while managing the protein-restricted diet.			No	
208	committee-discussion	People with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet	Poor taste and disagreeable smell and texture of low-Phe foods and synthetic protein substitutes. These have to be taken in large volumes 3 to 4 times a day and can cause digestive problems.	The are also full of sugar to make them more palatable which causes tooth decay. Major discomfort and distress for the sufferer and more expense for dental treatment through no fault of their own.			No	
209	committee-discussion	People with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet	They also need to educate professionals, teachers, other children's parents, their families, and other carers about PKU and the diet restrictions.	My daughter's nursery does not have the resources in the kitchen to manage her diet, so I have to prepare all of her food on behalf of the nursery.			No	
210	committee-discussion	There is a need for a treatment that can reduce PKU symptoms and give people with PKU and their carers peace of mind about blood Phe levels	The committee concluded that there is a need for a treatment that can reduce PKU symptoms and give people with PKU and their carers peace of mind about blood Phe levels.	For all people with PKU, not just children with PKU.			No	

211	committee-discussion	The estimate of 71.2% reduction in protein-restricted diet is not evidence-based	The committee concluded that it seemed likely that patients would reduce their protein-restricted diet, but it could not be certain that the reduction would be as high as 71.2%.	What threshold would the committee consider a reasonable enough reduction to place more value on the outcome?			No	
212	committee-discussion	The model time horizon is not long enough to capture long-term brain damage and the model is not appropriate to capture the effects of PKU in pregnancy	he model time horizon is not long enough to capture long-term brain damage and the model is not appropriate to capture the effects of PKU in pregnancy	This is a confusing decision; so you are discounting the effect of long-term brain damage and the effects of PKU in pregnancy because there isn't enough evidence even though it's widely accepted that both states are a major issue in the management of PKU long-term?			No	
213	committee-discussion	The utility values from the time trade-off study are highly uncertain, but are the only available evidence	The ERG and clinical experts acknowledged that quality of life is difficult to measure in people with PKU because of small patient samples and range of disease states.	So you accept that you can't measure quality of life in people with PKU, but your decision is that quality of life is not significantly improved enough to offset the cost of Kuvan. If QOL hasn't been determined then how is it possible to determine that Kuvan doesn't sufficiently improve it?			No	
214	committee-discussion	The utility reductions estimated for learning disability are not captured appropriately in the model	Furthermore, the committee noted that the long-term effect of brain damage from uncontrolled blood Phe levels cannot be captured in the model because of the 1-year time horizon.	Without capturing the long-term effect of brain damage from uncontrolled blood Phe levels, how is it possible to determine that quality of life is not significantly impaired, and therefore conclude that kuvan is not cost effective?			No	

215	committee-discussion	The methods used to calculate health state utility values are inappropriate and make the utility values highly uncertain	The clinical experts pointed out that there are patients with severe PKU symptoms and an IQ below 50, but with good care provision their quality of life would not be expected to be so poor as to be close to death. However, 1 patient expert confirmed that they are aware of a patient with severe symptoms and a learning disability who has communicated that they wish to die on several occasions. In addition to the unrealistically low values	This is a subjective statement. It is not for the committee to decide if facts are realistic or not. Facts are facts.			No	
216	committee-discussion	The methods used to calculate health state utility values are inappropriate and make the utility values highly uncertain	The committee concluded that the company's methods used to calculate health state utility values were inappropriate and make the utility values highly uncertain.	Subjective judgement used to dismiss facts and therefore support the conclusion (which is misguided and based on subjective judgements by the committee).			No	
217	committee-discussion	The additional utility gains modelled by the company for all women of childbearing age are not supported by evidence	However, avoiding harm to the developing fetus was clearly important, and the committee welcomes comments and further evidence on the potential use of sapropterin in women with PKU of childbearing age, or those planning pregnancy, to prevent harm to the unborn child.	While harm to the unborn child is entirely relevant, and has been proven, this dismissal of the experiences of women of childbearing age is discriminatory. The cost and unknown duration of being on an onerous and expensive pre-conception diet is an extraordinary burden to place on women who are trying to conceive. You are therefore making a discriminatory decision in discounting the fact that, without treatment, some women may not be able to consider pregnancy as an option and are therefore denying them their right to reproduce.			No	
218	committee-discussion	The costs of long-term brain damage and damage to the unborn child in pregnancy may be substantial, but these have not been modelled	However, information on long-term brain damage because of PKU is not routinely collected in the NHS.	But information on the cost of long-term brain damage must be routinely collected in the NHS and could be applied.			No	

219	committee-discussion	Sapropterin has not been shown to be cost effective in adults with PKU		The value of 'quality of life' has been underestimated in this decision to suit the conclusion that adults should not be prescribed Kuvan. 'The risk of irreversible damage' does apply to adults up to the age of 25, also the indirect risk of irreversible brain damage does apply to women who are at risk of maternal PKU syndrome, and therefore their child is at risk or irreversible brain damage.			No	
220	committee-discussion	The committee is unable to consider women who are pregnant or planning to conceive separately, and welcomes further comment and evidence on this group	the benefit to the unborn child	This needs to be considered alongside to the benefit to the woman pre-pregnancy, during pregnancy and as a mother.			No	
221	committee-discussion	Sapropterin is not recommended in adults with PKU for treating HPA that has been shown to respond to sapropterin	there is no corresponding increase in quality of life	this is a subjective judgement that has discounted the reality of adults living with PKU. PKU is for life, not just childhood and the decision to cease treatment at the age of 18 - before the brain has finished developing and at a crucial time in a young adults life - is discriminatory against age.			No	
222	committee-discussion	Sapropterin is not recommended in adults with PKU for treating HPA that has been shown to respond to sapropterin	Therefore, it concluded that sapropterin is not recommended in adults with PKU for treating HPA that has been shown to respond to sapropterin.	In making this decision you are setting a precedent that - the next time there is a breakthrough in PKU treatment - adults with PKU do not deserve access to treatment because the quality of life of an adult with PKU is not significantly enough impaired. This shows a complete lack of understanding of the reality of living with PKU at any age.			No	
223				The fact that studies have shown that there may be a link between pku, parkinsons and dementia due to the effect phenylalanine has on the brain to say that adults show no signs of irreversible brain damage is a incorrect thing to imply, NICE simply don't understand the condition. Pku is a horrible thing to live with, every week I suffer with anxiety, depression and other related mental health conditions. From my experience with PKU it has gotten worse as I've gotten older adults need help. The NICE is giving up on a generation of pku sufferers because we aren't worth the money it's absolutely disgusting. Taking this medication off 18 years is also one of the most ridiculous things I've heard of, NICE are basically dangling a carrot here, they are giving those children hope by allowing them to be the best they can be and then taking it away from them when they need it the most, imagine being stripped of your knowledge, common sense and mental health all when leaving home. I appreciate that children will benefit for a part of their life however they will suffer massively in their future just like adult pku sufferers are now.			No	

224					Has all of the relevant evidence been taken into account?	No	No	
225					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	No	No	
226					Are the recommendations sound and a suitable basis for guidance to the NHS?	No	No	
227					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	No	No	
228				I welcome the recommendation that children can use Kuvan but I believe that patients of all ages with PKU who respond to treatment with Kuvan should be able to use this medicine. I write this as a friend of an adult with PKU: In the interests of confidentiality I am referring to my friend as "Charlie", although this is not actually her name... I met Charlie about 5 years ago. We were both new employees at the same workplace and of a similar age (35-40ish). Charlie came across as being vivacious and seemed very eager to make new friends. Charlie explained about her condition (as she must have to do with almost every person she meets) and the limitations it puts on her day-to-day life, but she seemed determined for it not to define her. I imagine she was relishing the opportunity for a new chapter in her life and I admired her for that. We quickly became friends. We socialised together, often going for staff drinks after work. Charlie initially joined in as much as anyone else, she is really quick witted and highly intelligent - great company and good fun. Obviously she had to limit her alcohol intake, but then there was always the question of, "should we go for something to eat?" Charlie always visibly shrunk at this stage, not wanting to make a fuss, but also knowing full-well she was going to have to deal with the "why can't you eat this or that?" conversations and the inevitable looks of incomprehension, suspicion or fatigue as to, "why is she making a fuss, it's just food?" from restaurant staff and colleagues who weren't aware of her condition. So then, again she'd have to explain herself... This is just one example of how PKU dampens Charlie's spirit on a daily basis. Charlie also suffers from mood fluctuations and brain-fog (which can make her hard to work with or relate to at times) and sometimes she appears depressed and un-focused. I know she struggles with romantic relationships. Although she has a high sex drive, she is very hesitant about having sexual relationships because she is scared of becoming pregnant and having to deal with the challenges of pregnancy with PKU and the possibility of having to raise a child with PKU also. Dating is a hugely stressful thing for her because it is so loaded, and I can see it causes her great emotional turmoil. Despite all of this Charlie manages her condition extremely well, she sticks to the diet religiously. She has great discipline and self-control, and as a result she is generally healthy, but I know she finds it			No	

very, very hard and very, very draining. Basically PKU rules her life.

It is desperately unfair that my friend has to continue to live a limited and anxious existence when medication exists that could drastically change her life.

In addition to this, Charlie has explained to me that NICE has not considered the problem of young people stopping treatment with Kuvan on their 18th birthday. Managing phenylalanine levels with dietary treatment alone is very difficult, especially for teenagers leaving home, starting work, and establishing themselves as adults in the world. 18 year-olds accustomed to a very relaxed diet through using KUVAN will not have the coping skills to switch to a strict diet which involves constant preparation of meals, precise measurement of all foods, constant management of prescriptions, regular self-administered blood tests, and difficulties in participating in social occasions based around food, including eating out in restaurants. It will lead to people not continuing the diet, being lost to treatment and having health issues related to high phenylalanine levels in adulthood. NICE has ignored this issue completely.

NICE's analysis underestimates the benefits of KUVAN treatment for adults with PKU. NICE says there is no risk of permanent damage to the brain after the age of 18, but this is contradicted by other statements made by NICE in the document which recognise that permanent harm can occur after the age of 18 and that brain development continues until age 25. There is good evidence that many adults with PKU have very serious symptoms caused by high phenylalanine levels in adulthood. These problems in adults are undervalued by NICE. Furthermore, new research into neuroplasticity and more recently neurogenesis is showing more clearly that the brain continues to change and develop throughout life. NICE has ignored that the adult brain does not stop changing and developing.

NICE has not considered the harm of Maternal PKU Syndrome and the worry this can cause to women with PKU throughout their lives until the menopause. When deciding that Kuvan is not cost effective in adults, NICE has ignored the benefits to women with PKU of using Kuvan to help them have happy intimate relationships without having to worry about an unplanned pregnancy resulting in Maternal PKU Syndrome, and have safe and happy pregnancies, whether planned or not. NICE has recognised that controlling phe levels is important in early pregnancy, ideally before conception, and has recognised that this would reduce the risks of Maternal PKU Syndrome. However, the harms to mother and child from high levels in early pregnancy have not been included in the cost analysis. The mental and physical experiences of women with PKU who have gone through the pre-conception diet and a pregnancy, a time when hormonal changes and other health changes due to pregnancy are significant, have not been taken into account. Pregnancy can also result in severe illness that makes the diet even more difficult both mentally and physically. All of these difficulties and more are articulated by PKU patients in Ford, O'Driscoll, and MacDonald, 'Reproductive Experience of Women Living with PKU', Molecular Genetics and Metabolism Reports 17 (2018), pp.64-68, which NICE needs to take into account. The hormonal changes experienced by women during the menopause should also be taken into account as more early treated adults go into middle age: women need help to ensure they can maintain low phenylalanine levels throughout life. I believe that NICE has failed to take account of the issues experienced by women with PKU and that this is a major failing in the draft guidance.

NICE has ignored that many adults with PKU who have problems associated with high phenylalanine levels – like brain fog, depression, or poor memory – simply cannot cope with dietary treatment. The NHS should not leave people without a realistic option for treatment. Also, many adults who experience difficulties were told by the NHS when they were children in the 1970s-1990s that they did not need to continue the diet in their late teenage years and in adulthood, and so didn't, trusting their clinicians. The NICE draft guidance does not take into account that they were advised in this way, and that Kuvan would help them control their phenylalanine levels.

I also believe that NICE has undervalued the work and impact that managing PKU can have on adults with PKU and their families. People with PKU spend a lot of time looking after themselves and controlling their diet, or suffering the symptoms of high phenylalanine levels. This is clear from studies such as Ford, O'Driscoll, and MacDonald, 'Living with Phenylketonuria: Lessons from the PKU Community', Molecular Genetics and Metabolism Reports 17 (2018) pp.57-63 which gives a detailed account of the lived experiences of people with PKU. Also, the draft guidance does not take into account the positive economic, health, and social impacts of having more people working and achieving more in their careers, contributing to their communities, and being more active members of society, all of which would be possible with their phenylalanine levels better controlled through the

				use of Kuvan and any other new treatments that are created to treat PKU. People with learning disabilities are at a higher risk of being unable to control their phenylalanine levels with dietary treatment. The need for help with dietary treatment might also restrict the independence of people with learning difficulties. NICE recognised that people with learning difficulties might struggle with dietary treatment but there is no evidence that this has been included in the cost analysis in this consultation document. NICE has recommended using KUVAN at a dose of 10mg/kg. I agree that clinicians in the UK will prescribe more efficiently than in the US and that an average dose of 10mg/kg is appropriate for the cost analysis. However, I believe that clinicians should be able to prescribe within the marketing authorisation, which ranges from 5mg/kg to 20mg/kg. I believe that all people with PKU should have access to Kuvan on the NHS, and all future treatments for PKU that become available should also be funded to enable people with PKU to live freer, happier lives, and fulfil their potential.				
229					Has all of the relevant evidence been taken into account?	No. There is no evidence from UK trialists who took the drug for 5 years and then had it taken away. This is a key group that should have been considered. The account of these trialists who since restarting KUVAN has also been ignored. Additionally, evidence is hard to come by when PKU has no patient registry. When individuals are so spread around the country and get varying degrees of care and information. We are so rare that we often know more than the GPs who are our fist call when our PKU clinics are overwhelmed with needs within the PKU community, This is not a criticism. GPs are not update and meet our concerns with 'I am sure that is not your PKU' and yet - thanks to social media PKU adults are becoming more and more aware of their shared experience with high levels. This counts for nothing because we are rare and the questions are not officially asked in a country where we all avoid 80% of food and it either works or doesn't.	No	
230					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	No - the evidence is not representative because no one has asked the UK trialists who had it for 5 years. The cost of healthcare requirements for adults who are unable to adhere. Co-morbidities and senior healthcare. Not to mention factoring in the cost of DLA and additional benefits needed when they are unable to work.	No	

231					Are the recommendations sound and a suitable basis for guidance to the NHS?	No - taking KUVAN at the age of 18 will cause more harm than good.	No	
232					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	Females - childbearing age having just had KUVAN take from them is setting them up to fail completely. Over 18's - age discrimination.	No	
233				Reversible neurological changes in adults. Reversible - through levels below 200 (Shawn E Christ) which is incredibly difficult and requires the control needed in preconception and pregnancy. You are therefore suggesting that adults need to adjust their protein intake to reverse the damage that they will most likely suffer as a result of being unable to adjust to life on a fifth of the protein they consumed as a child. At a time when their life will be going though huge changes.			No	
234	recommendations	1 Recommendations	appropriate to stop.	It will never be appropriate to stop once started. When I stopped KUVAN and the trial ended - my life fell apart and I was unable to focus. My mood deteriorated significantly and I suffered from depression and anxiety. My work and relationships suffered as I was unable to control my levels and adhere to the original 12g of protein a day. Without BH4 - Adults will struggle or be unable to make the neurotransmitters, such as dopamine and serotonin, essential for mood regulation and healthy brain function. The ability to feel happy. When I was not on Kuvan, I would regularly have dark thoughts. I was constantly unhappy and every day was an act with a mask. The change in terms of protein allowance is very tough but more so is the shroud of 'brain fog' that encapsulates you. Most adult PKUers are on some form of anti depressant. BH4 has been used as a treatment for chronic depression (Dr. Lisa Pan 2011) that did not respond to regular treatments. Taking KUVAN from youngsters is an assault on their mental health. and this should be more of a concern that how their plate will look different.			No	
235	recommendations	1 Recommendations	brain function in adults	And yet, this is ignored. Having had KUVAN for 5 years during the inital UK trial and then having it taken off me, I know the exact detrimental impact this will have on the mental health of those who have it withrdrawn at the age of 18. During the decade after the trial I was unable to get a grip on the reduction to 12g of protein and I felt that I had lost control over my ability to concentrate, look other in the eye and carry out my role as mother and teacher.			No	
236	recommendations	1 Recommendations	reduces the need for a protein-restricted diet	I have gone from 12g of protein a day to 60g. I feel regenerated, I have not used any prescription foods since re-starting Kuvan. The saving on dietary cost here is huge. Not to mention the future clinics and professionals that will be required to deal with the co morbidities both physically and mentally that arise through a complete change in diet and lifestyle.			No	
237	recommendations	1 Recommendations	affects quality of life.	This is because no one has officially asked people who had it taken from them! You have used evidence from Biomarin to come to your current recommendation. I doubt that they have explained how taking it from all of the UK trialists, after 5 years, had a devestating impact upon their life. Each one!			No	

238	recommendations	1 Recommendations	no extra increase in quality of life	How has this conclusion been made? It is incorrect. We have not been asked. I was suicidal for years and I couldn't even explain why. I had a breakdown because I could not think clearly enough to make my life work on 12g a day alongside working and being a mum. I know many PKUers of my generation who are/ have also been suicidal - and this is something that has started as an adult when levels have been at their highest.			No	
239	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	reversible neurological changes in adults	I disagree. Going from 60g of protein to 12g or less a day is not compatible with adult life if you expect adults to be contributing members of society and perhaps even just live a happy fulfilling life - not necessarily be viewed as 'successful' . Where will they find the 19hours + need to maintain their newfound strict dietary control? They won't and they will silently and slowly fall into chronic anxiety and depression, their cognitive abilities will suffer and they will present with a myriad of other conditions as a direct result of high levels. Removing KUVAN at the age of 18 will cause neurotoxicity and white matter changes and THAT will only be reversible with a return to treatments such as KUVAN.			No	
240	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	This diet should be continued as an adult	Yet your proposal removes the need for strict dietary control and then expects a instant switch at the age of 18. This is not logical. There will be a complete lack of management skills and experience. This will not be possible for many adults who are expected to continue with their responsibilities and be thrown into a life of counting, measuring and testing. The additional time needed on a daily basis will have to come from somewhere and will impact upon study/work and QOL.			No	
241	committee-discussion	High blood Phe levels in pregnancy can have harmful effects on the unborn child	Early control of Phe levels, ideally before conception, would reduce the risks.	Yes ideally - though not all women can function on 2g of protein a day needed to do this for months on end while trying to conceive. Then comes morning sickness and nausea and the amino acid substitutes on top. The very thing that unites PKUers is a variable - protein tolerance. Those who respond to KUVAN should be given every opportunity for healthy conception and pregnancy. Data exists for healthy pregnancies and the majority of those women would have had higher tolerances at the start. In removing KUVAN for women of childbearing age, you are creating a huge barrier and endangering the life of unborn babies. 'Ideally' how will these women maintain low enough levels after 18 years of being on KUVAN.			No	

242	committee-discussion	People with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet	These have to be taken in large volumes 3 to 4 times a day and can cause digestive problems.	and problems with tooth enamel erosion and increasingly, gallbladder issues. I nearly died from a necrotic gallbalder after years of digestive issues/acid reflux and months of pain - all down to the acidic formula I took. I was too anxious to go to a doctor to be checked out.			No	
243	committee-discussion	There is a need for a treatment that can reduce PKU symptoms and give people with PKU and their carers peace of mind about blood Phe levels	Children with PKU frequently experience difficulty with focus, depression or anxiety, disordered eating, digestive problems, headaches, low mood and sadness, feeling tired all the time and being in a heightened emotional state (including aggressiveness, psychosis and paranoia) because of high Phe levels.	Adults suffer from this too? After exposure to high levels over time. There are lots of journals out there documenting this - but the research has been done in the USA and should be taken into account. The research does not exist in the UK because those PKUers who are out of the system do not get in contact with their clinics. There is no patient registry - yet PKuers (thanks to social media) do reach out to others. Their stories are harrowing - nut no one listens and no one joinst up the dots. Relationship breakdown/ losing access to children/ job losses/ eating disorders/ depression/ anxiety/ gastrointestinal issues/ obesity/ mental breakdowns/ phobias. if someone would listen - the evidence and experiences are there.			No	
244	committee-discussion	Sapropterin is clinically appropriate and beneficial for people with PKU that responds to sapropterin	The committee concluded that sapropterin is beneficial for those people with PKU that responds to sapropterin.	Everything above is also beneficial for adults - quality of life is important at a time when you are going out into the real world and wanting to start a family of your own and/ or begin a career.			No	
245	committee-discussion	The trial evidence shows sapropterin plus protein-restricted diet is clinically effective compared with protein-restricted diet	However, none of the RCTs were included in the company model because of their short duration and small sample sizes.	I was on it for 5 years - as were 8 other UK trialists and no one asked us anything. We have so much to say and we have all experienced similar issues since stopping the treatment. We have all experienced the same benefits being back on it. There are only 8 of us. Why can data and research from other countries not be used? We are all human with the same condition.			No	
246	committee-discussion	The estimate of 71.2% reduction in protein-restricted diet is not evidence-based	. The committee concluded that it seemed likely that patients would reduce their protein-restricted diet, but it could not be certain that the reduction would be as high as 71.2%.	A 3.2% difference is not enough to mean anything? This is ridiculous give the fact that it is even stated above that there is not a lot of evidence for you to consider in general. I could have 60g of natural protein and 20g from substitute at the moment and stay within safe levels. many on the trial could give u substitute completely. We are focusing on 3.2% of quantitative data and ignoring the qualitative life experience of adults here. Where is the focus on mental health rather than food increases and substitutes? The amount of suicidal struggling PKU adults out there is alarming. Individuals who feel themselves			No	

				slowly disintegrating and float further away from clinics out of embarrasment. There is no data to show this because no one has sought it.				
247	committee-discussion	Long-term brain damage in children is an important aspect of PKU, but there is little evidence to estimate its effect on quality of life	Long-term brain damage in children is an important aspect of PKU, but there is little evidence to estimate its effect on quality of life	Is this a typo? The thre bullet poits underneath will not affect quality of life? The human bran does not stop developing and regenerating at the age of 18. I developed white matter changes after a completely clear childhood scan. Well treated as a child - did well at school. At the age of 18 i started to struggle to adhere and within a couple of years I was suffering from phobias/panic attacks and dark thoughts. This is extremely common within the PKU community - but no attention is brought to it. The proposal is going to give children 'super powers ' for 18 years - no need to develop skills in managing life on just 6g a day - and then pull the rug from under them when they need focus, drive and mental clarity as they become an adult. PKUers young and old see this proposal is flawed and is in fact stockpiling a huge issue for the future.			No	
248	committee-discussion	Long-term brain damage in children is an important aspect of PKU, but there is little evidence to estimate its effect on quality of life	The committee concluded that long-term brain damage is an important aspect of PKU, but there is little evidence available to estimate its effect on the quality of life of people with PKU.	This is because no one has asked those that have been well treated and then struggled as an adult. We are glossed over. There is no evidence because there is no registry and no follow up to those who are out of the system. Those sitting at home with a mental and physical health problems that have developed since their levels have slowly crept up in adulthood. PKU and adulthood is not compatible.			No	
249	committee-discussion	The costs of protein-restricted diet estimated by the company are reasonable, but the cost savings with sapropterin are uncertain	The committee concluded that the cost savings related to a reduction in protein-restricted diet are uncertain.	So there needs to be a focus on all the c-morbidity issues in the PKU adult population. Those who struggled to adhere in adult hood: Add up the cost of prescription foods; prescriptions for antidepressants; anti-psychotics; operations to remove gallbladders (I personally know 5 PKUers who have had removals in the last 3 years) the loss of income (taxes) on people who have had to go part time; dental costs; clinic costs; cost of DLA payments and other benefits when they become unable to work; The cost of care when these people present in care homes needing round the clock care due to seizures, confusion, immobility and inability to do the most basic of tasks. These are all things that present in older PKUers due to the degenerative effects of neurotoxicity. We know this but it is not reported on because we are too slow to join the dots in the UK.			No	

250				I would like to make comment on my concerns regarding the restricted dosage, surely it is down to a trained prescriber to determind how much of a medication is needed by a patient. Some patients will need more than the maximum allowed dose currently proposed and it feels unjust that they will not be able to access enough of the approved drug to make a real difference. I would also like to make comment on the age restrictions. Again, this feels discriminatory why can an adult not have access to an approved drug? What will be the effects on a child who takes the drug up until their 18th and then have to stop? Thank you.			No	
251				1. A dose of 10mg/kg is not sufficient. In some cases, a dose of 20mg/kg may be required in order for the medication to be effective and clinicians should have the flexibility to prescribe a dose based on individual cases. 2. Kuvan should be approved for all age groups. The NHS recognises that PKU is managed by a controlled diet for life, not just until 18 years old. The symptoms are serious and significant for both adults and children. 3. There will be a significant and concerning impact by withdrawing Kuvan when a child reaches the age of 18. These individuals will have to cope with transitioning from benefitting from medication to control their condition, to having to solely rely on controlling their diet to avoid any symptoms of side effects.			No	
252					Has all of the relevant evidence been taken into account?	-	Yes	Inherited Metabolic Dietitians at University Hospitals Birmingham NHS Foundation Trust
253					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	-	Yes	Inherited Metabolic Dietitians at University Hospitals Birmingham NHS Foundation Trust
254					Are the recommendations sound and a suitable basis for guidance to the NHS?	No.	Yes	Inherited Metabolic Dietitians at University Hospitals Birmingham NHS Foundation Trust

						1) Discrimination on age 2) Discrimination on pregnancy. 1) Age: We are very concerned that the recommendation is only up to 18 years and after this time it will be discontinued. - The European guidelines (van Wedberg et al 2017) Statement #8 – Treatment for life is recommended for any patient with PKU. Why are you saying to stop Sapropterin at 18y? It is discriminating by age. We are concerned that it is not ethical to stop Sapropterin at 18 years. A young person's brain is still developing, they have big changes in their lives at this time e.g. leaving home, starting university, starting a new job. They will be leaving the support of their parents / carers who will have always managed their treatment and diet. During this time it is very important for the young person to keep their phenylalanine concentrations as low as possible for good executive functioning, to be able to concentrate and study, perform at work and maintain good relationships with people. If they then have Sapropterin stopped at 18 years, then their phenylalanine concentrations will rise. They will either have to suffer the consequences of high phenylalanine brain concentrations or adopt a stricter low protein diet. There is no other medical condition where a drug is taken away at 18 years and the patient expected to be able to manage a stricter complicated diet without it. - Even though little published evidence of irreversible brain damage in adults, it is only reversible if the patient can follow the low phenylalanine diet to keep phenylalanine concentrations low – but many patients can't manage this. Dietary treatment does not always prevent cognitive impairments in adults (Palermo et al 2017). Even patients that maintain good metabolic control struggle with emotional difficulties at sticking to the restrictive diet (Palermo et al 2020). Many adults struggle to control their diet when they work full time or shifts (Riva et al 2017), but many do not want to work part time as they lose out financially. - To understand the restrictive and challenging nature of the diet, then you would need to follow it for at least a week. The low phenylalanine diet is very restrictive, socialising and going out for meals is extremely hard. Taking a bitter tasting protein substitute 3-4 times per day is difficult and embarrassing. We often find this extremely complicated diet leads to disordered eating, guilt and anxiety about food (Antisdel & Chrisler 2000). Some adults can't do the diet, they can't stick to the low protein foods and can't take the drinks for long periods of time. In an audit of our adult PKU patients (150 following the low phe diet) in 2016 only 42% were achieving the target phe concentration of a median phe of less than 600umol/l, 43% were achieving a median phe levels of 600-1000umol/l and 16% had a median phe of over 1000umol/l. This shows how difficult the diet is to maintain phe concentrations in strict target range. - We have a case of an adult with irreversible brain damage		
255					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?		Yes	Inherited Metabolic Dietitians at University Hospitals Birmingham NHS Foundation Trust

						We have a 50 year old PKU patient (treated from birth) who was off diet since his teenage years who has developed spastic paraparesis and extensive cerebral white matter change 4 years ago. He has been on a strict low phenylalanine diet for the last 4 years (phenylalanine concentrations under 600umol/l) but this has not reversed the paraparesis. He is one of our oldest PKU patients treated from birth. We do not know if other adults with PKU will end up in the same situation if they cannot control their phe concentrations. We do not agree with stopping the treatment at 18 years and believe it should be available throughout life. 2) Discrimination on pregnancy and maternity: Preconception and Pregnancy – We are concerned that Sapropterin is not being offered as a first line treatment for ladies who are responsive to Sapropterin for pre conception diet and diet throughout pregnancy. The unborn babies to ladies with PKU are potentially being exposed to high phenylalanine concentrations which is similar to new born babies with PKU – yet you are treating them differently. There is good evidence that high phe concentrations are tetragenic and can result in maternal PKU syndrome (microcephaly, mental retardation, cardiac defects, spontaneous abortion and low birth weight) (Lenke & Levy 1980, Koch et al 2003, Lee et al 2005). Bringing down phe concentrations to a very strict range of 120-360umol/l (van Wedberg et al 2017) decreases the risk considerably, but to do this via diet is very hard and restrictive. Not only thinking about decreasing phe intake to only 150mg per day (~3g natural protein), but to ensure adequate calories and taking bitter tasting protein substitutes 3-4 times per day, every day, while suffering from morning sickness and hormone changes. A lot of ladies struggle with this, putting their baby at risk with higher phe levels. We currently can use Sapropterin as a second line intervention when they can not reach their target safe phe concentrations with diet, but the lady is so overwhelmed already and trying so many different strategies, that we cannot tell if it is working or not. The lady needs to be tested for Sapropterin responsiveness before they are pregnant to know if it works or not. It has been shown that the use of Sapropterin in pregnancy is safe and prevents the maternal PKU syndrome (Feillet et al., 2014; Grange et al., 2014). If phe levels remain high when they conceive or throughout their pregnancy then the child often needs extra support at school and assessment and support from speech and language therapists. ~50% of our ladies have unplanned pregnancy and their phe concentrations are too high when they conceive. If they were already on Sapropterin, their phe concentrations would be lower at conception. Once ladies have given birth, if their phe concentrations rise again then this will impact on how they care for their new born. They often cannot manage the strict diet while sleep deprived and		

						caring for a young baby and their phe concentrations rise. We believe that Sapropterin should be available throughout life (not stopped at 18 years) to ensure that ladies who are responsive can have the benefit of managing their phe concentrations more effectively and decrease the risk of maternal PKU syndrome in their babies. If it is not available throughout life, then we would suggest all ladies of child bearing age should be assessed for Sapropterin responsiveness and then offered it as a first line treatment when they are planning a pregnancy or pregnant, plus a year after while they are trying to cope with looking after a newborn.		
256	recommendations	1 Recommendations	they are under 18	We are pleased that NICE is recommending that Sapropterin for children as this benefit responders to be able to have a less restrictive diet and be able to eat more natural protein.			Yes	Inherited Metabolic Dietitians at University Hospitals Birmingham NHS Foundation Trust
257	recommendations	1 Recommendations	There is also no risk of irreversible brain damage in adults with PKU	- Even though little published evidence of irreversible brain damage in adults, it is only reversible if the patient can follow the low phenylalanine diet to keep phenylalanine concentrations low – but many patients can't manage this. Dietary treatment does not always prevent cognitive impairments in adults (Palermo et al 2017). Even patients that maintain good metabolic control struggle with emotional difficulties at sticking to the restrictive diet (Palermo et al 2020). Many adults struggle to control their diet when they work full time or shifts (Riva et al 2017), but many do not want to work part time as they lose out financially.			Yes	Inherited Metabolic Dietitians at University Hospitals Birmingham NHS Foundation Trust

258	recommendations	1 Recommendations	Also, there is not enough evidence on how sapropterin might be used to prevent harm to the unborn child in women with PKU who are pregnant or trying to conceive	See comments on discrimination above.			Yes	Inherited Metabolic Dietitians at University Hospitals Birmingham NHS Foundation Trust
259	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	However, adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25	Brain development does not stop until 25 years, then why are you stopping sapropterin at 18 years? At 18 years patients would then have to start a very hard restrictive diet that they are not used to to protect their brain.			Yes	Inherited Metabolic Dietitians at University Hospitals Birmingham NHS Foundation Trust
260	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	Clinical experts estimated that 10% to 20% of patients struggle to maintain control of blood Phe levels.	In our adult clinic, our last audit showed that only 42% of patients on the PKU diet were able to achieve a median phenylalanine of less than 600umol/l. This means 58% of those on diet struggled to maintain their the concentrations and their phenylalanine concentrations were above the European guidelines target range. This does not include people who are not on the diet as they can not manage it.			Yes	Inherited Metabolic Dietitians at University Hospitals Birmingham NHS Foundation Trust

261	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	Also, the timing, duration and intensity of exposure to high Phe levels in childhood and adolescence determine the severity of symptoms and long-term brain damage experienced by people with PKU.	These people are at a disadvantage as the brain damage done in childhood (as carers unable to manage the diet properly) means these people are unable to follow the diet in adulthood due to cognitive impairments. These are the people that would benefit the most from sapropterin.			Yes	Inherited Metabolic Dietitians at University Hospitals Birmingham NHS Foundation Trust
262	committee-discussion	High blood Phe levels in pregnancy can have harmful effects on the unborn child	They noted that good control of blood Phe levels (below 200 micromoles per litre) should be maintained if possible, but there are no strict guidelines or target Phe levels used in clinical practice.	This is not true. There are guidelines for PKU pregnancy. The European PKU guidelines (van Wedberg et al 2017) recommend for pregnancy that the mothers phenylalanine concentrations should stay between 120-360umol/l. In practice we would advise the ladies to keep their phenylalanine concentrations around 200umol/l.			Yes	Inherited Metabolic Dietitians at University Hospitals Birmingham NHS Foundation Trust
263	committee-discussion	High blood Phe levels in pregnancy can have harmful effects on the unborn child	However, the committee noted that about half of pregnancies are unplanned.	Sometimes the reason pregnancies are not planned is because the mother does not want to follow the strict difficult diet for months / years while trying to fall pregnant. Which is why it would be important for the ladies of child bearing age to be using Sapropterin if they are responders.			Yes	Inherited Metabolic Dietitians at University Hospitals Birmingham NHS Foundation Trust
264	committee-discussion	High blood Phe levels in pregnancy can have harmful effects on the unborn child	The committee concluded that high blood Phe levels in pregnancy can have harmful effects on the unborn child. Early control of Phe levels, ideally before conception, would reduce the risks.	Then why is it not being recommended for ladies of child bearing age? The difficulty is maintaining the difficult diet while struggling with morning sickness and hormone changes which increases the phenylalanine concentrations as they are catabolic. We would not see the same problems with a drug sapropterin.			Yes	Inherited Metabolic Dietitians at University Hospitals Birmingham NHS Foundation Trust
265	committee-discussion	People with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet	Clinical experts noted that just over 50% of adults with PKU are on a protein-restricted diet, while about 30% of adults have stopped their diet and the other 20% have difficulties maintaining it.	Even though patients say they are on diet, this does not mean they are able to reach target phenylalanine concentrations. (Only 42% of patients in our clinic who are on diet are maintain a phe less than the target range of 600umol/l. - this is based on the bloods spots they send back to us - so only snap shots in time and they may only be sending them in when they have been strict with their diet for a few days before hand).			Yes	Inherited Metabolic Dietitians at University Hospitals Birmingham NHS Foundation Trust

266	committee-discussion	People with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet	This can take 2 to 3 times as long as normal and make managing the diet a dominant activity of daily life.	Many adults struggle to control their diet when they work full time or shifts (Riva et al 2017), but many do not want to work part time as they lose out financially so suffer with high the concentrations.			Yes	Inherited Metabolic Dietitians at University Hospitals Birmingham NHS Foundation Trust
267	committee-discussion	People with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet	Costs of 'free-from'	Adults with PKU are disadvantaged as the free from foods they can buy from the shops are more expensive.			Yes	Inherited Metabolic Dietitians at University Hospitals Birmingham NHS Foundation Trust
268	committee-discussion	People with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet	The known risk of irreversible brain damage if Phe levels are not controlled is a permanent source of stress for carers. The committee concluded that people with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet.	All these stresses and worries are the same for adults with PKU as well. They are living the unknown as the oldest well treated is only in their late 40s / early 50s.			Yes	Inherited Metabolic Dietitians at University Hospitals Birmingham NHS Foundation Trust
269	committee-discussion	There is a need for a treatment that can reduce PKU symptoms and give people with PKU and their carers peace of mind about blood Phe levels	Additionally, adults with PKU may find it difficult to juggle work, studies and family commitments with controlling their diet and maintaining Phe levels. Some adults are unable to engage in full-time work because it creates a vicious cycle of less time to control diet and higher Phe levels, leading to reduced ability to focus and organise the diet. In addition, they can have a sense of being dependent on other people for support, feel socially isolated and constantly worry about maintaining their diet	You have stated why it is so hard for adults to follow the PKU diet and struggles they have when their phenylalanine concentrations are so high, so why are they not allowed it?			Yes	Inherited Metabolic Dietitians at University Hospitals Birmingham NHS Foundation Trust

270	committee-discussion	There is a need for a treatment that can reduce PKU symptoms and give people with PKU and their carers peace of mind about blood Phe levels	Mothers with PKU describe being unable to cope with the pressures of strict dietary management while caring for their child, and experiencing anxiety, depression and inability to focus as a result.	again, you have acknowledge the problems here and you are denying them the drug that could help solve these problems (for the responders).			Yes	Inherited Metabolic Dietitians at University Hospitals Birmingham NHS Foundation Trust
271				This is so bittersweet To approve this drug for children up to the age of 18 is amazing and life changing however then they reach the age of 18 and it will taken away potentially causing complications for patients in adult life. Appropriate dosage for individuals would be more effective and in the long run be a cost effective decision. PKU is not a life choice it is genetic and ethically should be treated as required on an individual basis and not with set dosage! This drug for PKU sufferers should be a life long treatment and not just for children up until the age of 18! These people will just be entering into adulthood with restrictions before they even begin! This is not a fair choice! Please review			No	
272					Has all of the relevant evidence been taken into account?	I don't think that all areas have been represented in the Consultation document at all. To merely consider babies and young adults for Sapropterin treatment is unfair. The whole PKU age range patients should be offered this drug.	No	
273					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	Not in my opinion, no! Just targeting the age range from 0 to 18 years only would be cruel. This diet is crucial to each PKU patient and it is not a life choice.! As all patients get older other problems will come into play, they may need Therapy, counselling, hospital stays, mental health issues, gastric problems to name just a few, and when they reach middle to old age more care - by extension a plethora of other drugs, this will cost the NHS more and more money in the long term. No one counts the cost when it comes to other medicines, nor is the age range considered to determine when they can and can't get their drugs.	No	
274					Are the recommendations sound and a suitable basis for guidance to the NHS?	I think that there is a lot of content but do not feel that all PKU adult patients, and their problems have been represented properly.	No	

275					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	I believe that providing Sapropterin(Kuvan) to PKU patients just up to the age of just 18 would discriminate against this very group as they age and also the older PKU patients and especially the over 40/50 age group and beyond. To give Kuvan up to just 18, when these patients are on the cusp of their adult life and at their most vulnerable perhaps, and then take it away and ask them to control their Blood levels and eat a very strict diet, which they have never been used to would be an absolutely dreadful thing to do to them. Many will fall by the wayside Also, it is virtually impossible to get the PKU diet in hospitals when PKU patients are in their care so how will this affect older PKU patients if, God forbid, they need care or nursing homes in later life? All age groups should be taken into account and not discriminated against when considering PKU patients' whole of lives.	No	
276					Has all of the relevant evidence been taken into account?	No because we are disabled without any family in the UK and we couldn’t manage my wife's diet.	No	
277					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	Because PKU has long life problem, please review your decision.	No	
278					Are the recommendations sound and a suitable basis for guidance to the NHS?	We not sure about that.	No	
279					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	Unfortunately yes as we both have disabled without any friends or families. And if someone like us will have baby without Kuvan and strict diet (we couldn’t provide strict diet as our disability) the baby will be disabled 100 percent and this, in addition to being a great injustice to the child, imposes a great cost on the NHS.	No	
280				Dear Sir/Madam My wife has pku and I am blind. As we couldn’t manage her diet at all we can not try to have a baby . Please consider our situation and add some Exception for families who couldn’t manage their diets. Thank you Mo&Fatemeh			No	
281					Has all of the relevant evidence been taken into account?	testing	No	
282				Testing testing 123			No	
283				How blinking stupid and irresponsible, by only allowing kuvan till the age of 18 you are encouraging people to come off diet as people will find it more of a struggle to transform to a low protein diet after spending the first 18 years of life not worrying about what they are consuming... just ask the many MPs how they found the pku diet for a day! I’m sure they will tell you how much of a struggle it is. Again. Why is it us adults who pay into the taxation system get ignored?			No	

284					Has all of the relevant evidence been taken into account?	yes	No	
285					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	unable to comment	No	
286					Are the recommendations sound and a suitable basis for guidance to the NHS?	in my opinion they need to be rethought in one or two areas	No	
287					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	age and sex	No	
288	recommendations	1 Recommendations	PKU is an inherited condition that causes raised levels of phenylalanine in the blood. Without treatment, this causes irreversible brain damage in babies and children and affects brain function in adults. The only treatment for PKU is a diet to manage phenylalanine and overall protein intake (protein-restricted diet). Sapropterin is used alongside this diet.	there are no trials to support how the quality of life is affected, yet adult sufferers of PKU will describe their symptoms and how it affects their ability to work etc. treatment should be continued past 18 years			No	

289	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	Clinical experts explained that brain development peaks at around age 12. After this high Phe levels are unlikely to affect IQ. However, adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25. In adults, high Phe concentrations can result in short-term symptoms, which are considered reversible by lowering Phe levels through diet. These include impaired executive function, reduced autonomy, impaired social maturity, difficulty forming relationships and neuropsychiatric symptoms such as depression, anxiety and inattention. Clinical experts estimated that 10% to 20% of patients struggle to maintain control of blood Phe levels.	evidence that treatment should be extended past 18 years			No	
290	committee-discussion	High blood Phe levels in pregnancy can have harmful effects on the unborn child	. One patient expert highlighted that there is an NHS policy in place for providing sapropterin for pregnant women with PKU. The NHS England commissioning expert and the patient expert indicated that the NHS policy only covers women with PKU who are already pregnant	this would deter women from becoming pregnant , discriminating against this group of patients			No	

291	committee-discussion	The only treatment option available for people with PKU is a self-managed protein-restricted diet	Current clinical management of PKU is through a lifelong protein-restricted diet. This consists of prescribed low-protein and Phe-free medical foods to help reduce natural Phe consumption, and Phe-free amino acid supplements to improve nutrition and prevent nutritional deficiencies. The protein-restricted diet also involves reducing natural protein consumption according to individual Phe tolerance.	this diet is unbelievably restrictive and will affect all aspects of life, social activities, school life and family get togethers. The current treatment tastes absolutely awful, perhaps the committee might try a sample diet and treatment for themselves?			No	
292	committee-discussion	There is a need for a treatment that can reduce PKU symptoms and give people with PKU and their carers peace of mind about blood Phe levels	Many adults describe the effects of high Phe levels as 'brain fog', forgetfulness, tiredness, confusion, low mood and feelings of irritability. This can affect their ability to control their diet and maintain adequate blood Phe levels. Additionally, adults with PKU may find it difficult to juggle work, studies and family commitments with controlling their diet and maintaining Phe levels. Some adults are unable to engage in full-time work because it creates a vicious cycle of less time to control diet and higher Phe levels, leading to reduced ability to focus and organise the diet. In addition, they can have a sense of being dependent on other people for support, feel socially isolated and constantly worry about maintaining their diet (see section 3.4). The committee understood that concerns about high blood Phe levels can also affect women's sexual and reproductive health and choices. In some cases, women completely forego sex	seriously affecting core aspects of daily living and human choices . Any treatment to improve this situation must be considered in the context of mental health rather than economic terms.			No	

			because they are afraid of becoming pregnant and accidentally harming their unborn child.					
293					Has all of the relevant evidence been taken into account?	I am the lead Specialist metabolic Dietitian at Sheffield Teaching Hospital Foundation Trust and am a member of the medical advisory panel of the NSPKU. We manage around 160 patient 16 and over with PKU. I do not agree with the decision you have made regarding adults and not to allow the NHS to treat them with Sapopterin on the NHS. You have not taken into account the professional experience of treating these patient day to day within the NHS and the issues patients suffer with this condition. Many of our patients suffer with anxiery, depression, mood swings, fatigue, poor executive functioning, stuggle to look after their family and have a job and perfrom well in it. We know that there are changes in the white matter of the brain in these adults but it is incnclusive what this means long term.Where the evidence isnt conclusive expert clinical opinion must be used to guide treatment, I would urge you to take further guidance from Consultant Metbolic Physicians treating patients over the age of 18. The evidence is conclusive that high Phenylylanine levels in preconception and pregnancy damages and is tetratogenic to the foetus, this drug needs to be avaiable to all women of child bearing age to prevent this from happening and the state and NHS having to pay for care of the damaged child for life.	No	

294					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	Commonly we see in our clinical practice in the NHS the negative effects of higher Phenylalanine levels eg over 600umol/l. Patients have anxiety, depression, mood swings, short term memory issues, poor executive functioning, difficulty performing well at work, some not able to work fully and affects this has on family life , bringing up their own children and relationships. The European guidelines 2017 recommend lifetime treatment so stopping Sapopterin at 18 years is not clinically indicated or beneficial. You wouldnt stop antidepressants or diabetic treatments. The heterogenicity of the adult PKU popluation makes them difficult to study and prove the side effects of high Phenylalnine levels but we see these effects commonly in practice. Patients currently transition to adult services like our at around 18 years old, this is a difficult time to get good Phenylalanine levels controlled as they may move away to universtiy or start work, have relationship, having to teach someone to go on a strict low protein diet is very difficult and time consuming so not only having to be done at a difficult age but using more NHS resoruces in the adult Metabolic centres than we currently have. Compliance to any dietary treatment is difficult long term, you only need to look at the Obesity issues within the UK to see that " being on a diet" isnt the answer. If it was that simple Doctors wouldnt need to prescribe statins to lower cholesterol as patients could commence on a cholesterol lowering diet for life. PKU is a rare condition and not all patients will response to Sapopterin so the costs to the NHS wouldnt not be huge compared to a patients with more common illnesses like Diabetes or heart disease. I believe you should consider the perecentage of patient who will respond to this drug and therefore the cost will be less to the NHS.	No	
295					Are the recommendations sound and a suitable basis for guidance to the NHS?	We routinely see in practice that if we get someone with PKU back onto the low protein diet and their Phenylalanine levels get into range there mental health improves, they have more energy, less anxiety and deperssion and more motivation. They are able to perform better at work, contribute to society better and look after their family better. The problem is that to maintain this long term is very difficult. This is why I feel Sapopterin should be avaiable to adult who respond to it. Mental health should be as imporant as physical health and therefore this drug should be a treatment option for all adults aged 18 plus. I refer to the "The NHS Five Year Forward View pointed out that one in four of us will experience mental health problems, and mental illness is the single largest cause of disability. Yet mental health services have for several decades been the ‘poor relation’ compared to acute hospital services for physical conditions." Fortunately there is now good evidence that tackling some major mental health problems early reduces subsequent problems, improves people’s life chances, and also saves money for the wider economy." This is your opportunity to improve the mental health of patients with PKU who respond to Sapatoterin.	No	

296					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	Within our caseload of adult patients with PKU we have some that are classed as vulnerable adults i.e: people with learning disabilities, downs syndrome, profoundly deaf, low IQ,psychiatric illness. The decision not to allow adults with PKU to be treated with Sapopterin discriminates against them. Many of these patients are unable to follow the strict diet requirements to keep Phe levels in range 120 to 600umol/l. Many find the anxiety that come with higher Phenylalanine levels hard to live with, afects there ability to work and lead a productive life even with family support. They will cost the NHS more in the years to come as they age than the cost of Sapopterin. This drug would revolutionalise their lives, helping them to be able to have a job and contribute to society without the mental health issues that high Phenylalnine levels brings on top of their disabilities. The other type of patient I feel this discriminated is the maternal PKU patient. I note the government launched" a call for evidence to improve health and wellbeing of women in England" on 6th March. The prescription of Sapapterin for all women of childbearing age who may become pregnant should be considered under this reform.The maternal diet is even stricter than the adult diet targets and very difficult to achieve and remain on while trying to get pregnant and throughout pregnancy. We do have around 60% of patients that get pregnant not on diet (similar the the general population) This exposes the foetus to heart malformations,brain damage, "maternal PKU syndrome". I would urge you to consider Sapopterin treatment for all women of childbearing age to prevent a child being born with maternal PKU symdrome and costing the state and NHS for the care in will need over its lifetime and also to reduce the burden that these women have to managed by controlling their Phenylalnine levels by diet alone.	No	
297				I'm not sure how you think it's ok to say under 18 year olds can have this drug but when they turn 18, they will be taken off it. This drug will change many children's lives but then when they become an adult they will have to go back to how life was before they had the drug. It is unethical.			No	
298					Has all of the relevant evidence been taken into account?	Doesn't read like it has.	No	
299					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	You mention cost effectiveness estimates - simply look at the cost of a child born with a learning disability (the outcome of an unplanned PKU pregnancy). I am sure these estimates are already out there and include medical appointments, Health and educational plans requiring additional support at school or specialist educational placements, lifelong access to carers.	No	
300					Are the recommendations sound and a suitable basis for guidance to the NHS?	You have said that carers of children with PKU also report additional difficulties related to diet management. These include strains on their relationships, struggling to get the right support, and having to give up work or working part-time to dedicate more time to diet management. They also need to educate professionals, teachers, other children's parents, their families, and other carers about PKU and the diet restrictions. The known risk of irreversible brain damage if Phe levels are not controlled is a permanent source of stress for carers. The committee concluded that people with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet. WHY ON EARTH ARE YOU THEN TAKING IT AWAY FROM THESE CHILDREN WHEN THEY TURN 18	No	

301					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	Maternity is a protected characteristic and many PKU women are unable to plan to have a family because to do so means controlling their phenylalanine in an almost impossibly narrow range. May I also bring your attention to the mental health effects on a woman who is unable to control her phenylalanine in a narrow range, or has an unplanned pregnancy and therefore has a child with severe developmental delay. The subsequent guilt and shame she will feel, most likely for her entire life and that of the child, should land squarely at the feet of NICE reviewers who have it in their power to protect the future children of women with PKU but are wilfully choosing not to.	No	
302	recommendations	1 Recommendations	they are under 18	Kuvan should be approved for all age groups. It should not be limited to just those under 18. This guidance underestimates the benefits of Kuvan treatment for adults with PKU. It says there is no risk of permanent brain damage after the age of 18, but this is directly contradicted by the statement that the brain continues to develop up until the age of 25. More recent evidence shows that brain development continues to develop well into old age. Many adults with PKU have very serious symptoms – such as depression, anxiety, brain fog and memory loss - caused by high phenylalanine levels. Protein allowance does not typically increase as patients get older and therefore dietary treatment and management only gets more difficult in adulthood. The NHS has also sine 1993 recognised and endorsed that dietary treatment is for life. PKU is not cured once a person turns 18. The draft guidance does not stipulate or consider the impact on a patient taking Kuvan in childhood and then having it withdrawn on their 18th birthday. These 18-year-olds are often at a crossroads in their lives at this point, for example going to university or leaving home. Managing phenylalanine levels with dietary treatment alone is very difficult, especially for teenagers. 18-year-olds accustomed to a relaxed diet through using Kuvan would not have the coping skills and tools to switch to an extremely restricted diet and would go on to suffer a whole host of issues and symptoms. This issue has been completely ignored in the guidance.			No	
303	recommendations	1 Recommendations	a dose of up to 10 mg/kg is used	Draft guidance says “a dose of up to 10 mg/kg is used”. This cap should not be in place. Clinicians should have the flexibility to prescribe the dosage according to individual patient needs and in line with the manufacturers authorisation which ranges from 5mg/kg to 20mg/kg. With this current guidance, there is a large risk that many patients would be classified as non-responders, when they in fact need the higher dose of 20mg/kg. This is the common practice in other countries. The costing against 10mg/kg is appropriate as that is likely to be the average dose, but clinicians need the flexibility to prescribe up to 20mg/kg where required. The decision to cap the dosage is purely a cost reason, not a clinical decision. All other countries don’t have this cap, so why is the UK recommending this?			No	
304				Whilst it is pleasing that this drug has finally been made available to children under 18, I feel that further consideration should be given to adults having access to the drug, particularly if it has been used successfully in childhood and is deemed clinically appropriate. Also should prescribed dosage be assessed on a case by case basis rather than setting an upper dosage limit?			No	
305				I am delighted that my friends 6 year old son Stanley has been granted Kuvan. This could mean a nearly free or free diet for him. This will ease the worry of his parents when he is out of their care (at school, parties etc). It is however, disappointing that this life changing drug will be taken away from him when he turns 18. To go from having a free diet to a very restricted one again is unthinkable. For many people with pku, there is just not enough flexibility to allow them a substantial diet without this drug. Also, the dose is set at 100mg each. I understand that this is to control cost but if everyone needing Kuvan were given the dose they require, it may work out to an average of 10mg anyway as each patient will require more or less. As I say, we are all delighted that this drug has been granted but the caveats in the document urgently need assessing so that every pku sufferer, of any age are able to live with a free diet.			No	
306				My daughter is 15 weeks old she has pku. I'm happy that you have approved pku for under 18s but its bittersweet because if she responds to kuvan at 18 she will have to go on a restricted diet. There is health and mental wellbeing that needs to be looked at also quality of life should be taken in consideration. I don't think it's fair to offer some people treatment and others no treatment everyone that suffers from pku should have the same opportunity to have a better life.			No	

307					Has all of the relevant evidence been taken into account?	Yes, but a lot of the evidence boils down to "we don't have enough data" which is somewhat understandable given how rare PKU is, but given how sapropterin is available in many countries without their healthcare institutions becoming bankrupt, the evidence becomes a lot harder to swallow.	No	
308					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	No, it seems to contradict the evidence quite a lot.	No	
309					Are the recommendations sound and a suitable basis for guidance to the NHS?	Absolutely not. The recommendations are ignorant at best and malicious at worst. Telling a patient at the age of 18 that they must continue normal diet when they have a lot going on is a lot of pressure and responsibility to place on someone. I know, because I was in a similar situation. I had ABC A Level Grades and BC AS grades, as well as 3A's, 5B's, 2C's for GCSE and got into University [redacted]. That's what I had to go through and I'd rather not anyone else have to go through that situation because they (rightly) accepted the freedoms of Sapropterin but suddenly have to reverse and re-learn the basics. Trying to manage the diet by myself, I got confused and eventually went "off diet", which lead to me retaking my first year and getting a 3rd (barely passing) my second year due to the lack of focus and attention. Getting these results left me riddled with anxiety and depression, and I had to go to the GP to get Propanolol (to reduce anxiety) and Domperidone (to allow myself to eat food). The notion that a patient's brain stops being able to be damaged at the age of 18 like some sort of immediate switch is a ridiculous notion made even more ridiculous there is nothing to back this claim up.	No	
310					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	Cutting off sapropterin to someone because they reached the age of 18 can be considered age discrimination and would be deemed unlawful.	No	
311	recommendations	1 Recommendations	is no extra increase in quality of life for adults	3.3 to 3.6 in this report counteracts this claim. Not only that, but as someone with PKU who has to deal with mood swings, anxiety, depression, loss of focus, irritability, and forgetfulness because of how error-prone micro-managing the diet is, I believe if Sapropterin does help reduce and maintain steady phe levels (and therefore reduce all of the effects above) then how is that not increasing the quality of life for adults? Moreso, most PKU adults have depdendents who they rely on to help them manage the burden of the diet. Having Sapropterin available for PKU adults would do *wonders* in relieving the burden of people who support PKU Adults, whether it is family, friends, loved ones, or co-workers. And what about social outgoings? I know I've personally avoided social outings with friends and even			No	

				family members if it means avoiding a restaurant with food I can't have because I don't want to take the risk of feeling the symptoms above.				
312	recommendations	1 Recommendations	to offset these costs	I've got the following on prescription: * Fate Low Protein All Purpose Mix (flour substitute) * Loprofin Low Protein Pasta Long Cut Spaghetti (spaghetti substitute) * Mevalia Low Protein Spaghetti (spaghetti substitute) * PKU Sphere 20 (protein supplement) * Promin Plus Low Protein Pasta Spirals (pasta spirals substitute) * ProZero Liquid (milk substitute) I'm sure if Sapropterin upped my levels of protein from 6g a day to 10g a day, I could easily ditch the ProZero. Up to 15g and I could easily greatly reduce what I order on prescription if not outright remove some of them as I would go and eat "normal" food (which is far more convenient and allows me to be sociable and flexible). Not only that, but given some of the mental health struggles I've faced with the diet, it would save a trip or two to the GP, so giving Sapropterin to PKU Adults multiplies as a mental health investment win.			No	
313				The document states that treatment would be stopped at age 18, if treatment is helping the young adults and reducing brain fog etc, the treatment should continue into adulthood. If the treatment is showing signs of improving that young adults life and is working for them, it justifies continuation of treatment. The document states: recommended dose of 10mg and yet there must be justification for up to 20mg and finding the correct dosage for the individual patient, to say the dosage would be the same for everyone is a blanket response and does not take into consideration the individual.			No	
314					Has all of the relevant evidence been taken into account?	No, no lived experiences have been taken in to account. Reduction in cost of less numbers of protein substitute or prescription food has not been analysed. Increased cost of needing to use mental health services due to high phe levels not considered.	No	
315					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	Nope as above	No	
316					Are the recommendations sound and a suitable basis for guidance to the NHS?	No, they are ageist and unethical	No	

317					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	Yes, by ceasing treatment at 18 is unethical and discriminatory of age.	No	
318	recommendations		the company provides it according to the commercial arrangement (see section 2).	Biomarin have lost their patent therefore cheaper options will be available			No	
319	recommendations	1 Recommendations	a dose of up to 10 mg/kg is used	This dose may work for individuals with milder cases of PKU who will also have higher protein tolerance anyway. By restricting the dose amount you are restricting those who have the most strict protein tolerance. Research has shown that doses of 20mg/kg are most effective.			No	
320	recommendations	1 Recommendations	they are under 18	incorrect. The effects of sapropterin do not stop once an individual turns 18. The age of 18 is likely the first age someone with PKU is in independent control of their diet, they will then have to learn how to restrict the diet further- thus increasing the chances of stopping diet. NHS recommend the diet is for life so why isn't the treatment??			No	
321	recommendations	1 Recommendations	There is no clinical trial or registry evidence to show whether sapropterin reduces the need for a protein-restricted diet or how it affects quality of life.	Speak to the individuals who are taking the drug either following clinical trials or through IFR! They will tell you the effect!			No	
322	recommendations	1 Recommendations	The dose of sapropterin is based on weight so costs are higher for adults than children but there is no extra increase in quality of life for adults to offset these costs	The quality of life will massively decrease upon ceasement of this drug if they are allowed a more flexible diet. The sudden reduction will cause people to come off the diet and an increase in mental health crisis'- thus costing more money and increasing demand on an already overdemanded service.			No	
323	recommendations	1 Recommendations	there is not enough evidence on how sapropterin might be used to prevent harm to the unborn child in women with PKU who are pregnant or trying to conceive	This is likely due to it being unethical to trial medication through pregnancy. However there is evidence that high phenylaline levels in pregnancy cause adverse effects to the developing foetus, again costing alot more money to fund the care the baby will need throughout their life.			No	
324	information-about-sapropterin	2 Information about sapropterin	The list price of sapropterin is £597.22 per 30-tablet pack. Each tablet contains 100 mg sapropterin dihydrochloride (excluding VAT; BNF online, accessed January 2021).	Also look at the price of the protein substitutes and prescription foods to compare the overall prices. Also, my son has a gastrostomy due to unpalatable substitutes- look at the price of the repeated surgeries and supplies of syringes, dressings etc for the health of his PEG.			No	

325	information-about-sapropterin	Marketing authorisation indication	Kuvan, BioMarin	Patent has been lost, allowing for cheaper production from other drug companies			No	
326	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	reversible neurological changes in adults	So because you believe the neurological changes are reversible in adults it is okay for them to suffer with neurological changes??			No	
327	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	there are currently about 2,000 people with PKU in NHS care in England.	There is a large number of people with PKU whom aren't in NHS care, therefore that suggests the restrictive diet is not a feasible treatment alone for PKU. If the diet was less restricted more individuals would be likely to engage with NHS services, thus improving their overall health			No	
328	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	reduced executive function (working memory, flexible thinking, and self-control)	This side effect continues the whole lifespan of the PKU affected human			No	

329	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	This diet should be continued as an adult.	So why should the treatment that lessens the restrictive diet be stopped			No	
330	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	One patient expert confirmed that there are adults with PKU in the National Society for Phenylketonuria (NSPKU) who have severe symptoms and irreversible brain damage	Limited consultation with patient experts if you are only consulting with 1			No	
331	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	These include impaired executive function, reduced autonomy, impaired social maturity, difficulty forming relationships and neuropsychiatric symptoms such as depression, anxiety and inattention.	These symptoms will cause reliance on social care services, NHS services and mental health wellbeing services. Which is extremely costly.			No	
332	committee-discussion	High blood Phe levels in pregnancy can have harmful effects on the unborn child	below 200 micromoles per litre) should be maintained if possible, but there are no strict guidelines or target Phe levels used in clinical practice.	European adult phe level guidance is up to 600. By reducing the guidance to 200 is cutting the individuals intake by 2/3.			No	

333	committee-discussion	High blood Phe levels in pregnancy can have harmful effects on the unborn child	The NHS England commissioning expert and the patient expert indicated that the NHS policy only covers women with PKU who are already pregnant who are unable to establish Phe levels that are not harmful to the unborn child (100 to 300 micromoles per litre) on a protein-restricted diet. Only then can they be tested for a response to sapropterin.	By the criteria being an unplanned pregnancy, women are more likely to have unplanned pregnancies in order access this treatment.			No	
334	committee-discussion	High blood Phe levels in pregnancy can have harmful effects on the unborn child	Clinical experts confirmed that the outcomes for pregnant women with PKU are better in the UK than other countries such as the US.	Could be due to individual behaviours rather than treatment, or better antenatal care in the UK.			No	
335	committee-discussion	High blood Phe levels in pregnancy can have harmful effects on the unborn child	Early control of Phe levels, ideally before conception, would reduce the risks.	Allowing adults to have the treatment would increase diet tolerance and thus reduce high conception phe levels			No	
336	committee-discussion	The only treatment option available for people with PKU is a self-managed protein-restricted diet	The committee concluded that the only treatment option available for people with PKU is a self-managed protein-restricted diet	Managing this diet has a massive toll on individuals and their families. It is isolating, many restaurants won't cook food suitable for PKU sufferers, you have to spend long amounts of time cooking, frequent liaising with GP's and pharmacies for prescriptions and liaising with dieticians. In my experience as a mother of a child with PKU, my mental health declined massively and affected the families quality of life. Look at the DLA and PIP claims to understand the toll following the diet has on life.			No	
337	committee-discussion	People with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet	Poor taste and disagreeable smell and texture of low-Phe foods and synthetic protein substitutes. These have to be taken in large volumes 3 to 4 times a day and can cause digestive problems.	My son has had to have a surgical feeding tube purely to administer this			No	

338	committee-discussion	Sapropterin is clinically appropriate and beneficial for people with PKU that responds to sapropterin	In addition, they were able to resume other activities such as studies or work.	Increasing life outcomes, people can hold jobs down and lessen the strain on the benefits system			No	
339	committee-discussion	Sapropterin is clinically appropriate and beneficial for people with PKU that responds to sapropterin	Carers of people with PKU reported a significant easing of burden of care. This included not needing to prepare special prescribed low phenylalanine foods and being able to delegate childcare to others for first time. Some carers reported being able to return to work or study, increase working hours, spend more time with other children, and have time for other family responsibilities.	This would be a dream. I am the sole carer for my son and I have had to change my career due to no one happy to care for his needs without me fully preparing food and planning his needs			No	
340	committee-discussion	Sapropterin is not recommended in adults with PKU for treating HPA that has been shown to respond to sapropterin	Therefore, for adults sapropterin is not within what NICE considers a cost-effective use of NHS resources. T	You earlier state that adults are more capable to function better, hold jobs and enjoy a life. By restricting this drug it is against human rights and is extremely unethical. This is ageist.			No	
341	appraisal-committee-members-and-nice-project-team	6 Appraisal committee members and NICE project team	George BraileanuTechnical leadJoanna RichardsonTechnical adviserThomas FeistProject manager	Do these people fully understand what its like to live with PKU or have a child with it? Especially in the removal of a treatment??			No	
342					Has all of the relevant evidence been taken into account?	No. I would argue that quality of life can only be measured qualitatively not quantitatively, therefore it is a poor scientific argument that there is no evidence out there. I am aware that patient personal accounts were sent to NICE to be reviewed as part of the evidence. This is your evidence - do your job and read it.	No	

343					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	Absolutely not. 1. Draft guidance says “a dose of up to 10 mg/kg is used”. This cap should not be in place. Clinicians should have the flexibility to prescribe the dosage according to individual patient needs and in line with the manufacturers authorisation which ranges from 5mg/kg to 20mg/kg. With this current guidance, there is a large risk that many patients would be classified as non-responders, when they in fact need the higher dose of 20mg/kg. This is the common practice in other countries. The costing against 10mg/kg is appropriate as that is likely to be the average dose, but clinicians need the flexibility to prescribe up to 20mg/kg where required. The recommendation to cap the dose at 10mg/kg for children is purely on cost, not on clinical effectiveness.	No	
344					Are the recommendations sound and a suitable basis for guidance to the NHS?	Absolutely not. Kuvan should be approved for all age groups. It should not be limited to just those under 18. This guidance underestimates the benefits of Kuvan treatment for adults with PKU. It says there is no risk of permanent brain damage after the age of 18, but this is directly contradicted by the statement that the brain continues to develop up until the age of 25. More recent evidence shows that brain development continues to develop well into old age. Many adults with PKU have very serious symptoms – such as depression, anxiety, brain fog and memory loss - caused by high phenylalanine levels. Protein allowance does not typically increase as patients get older and therefore dietary treatment and management only gets more difficult in adulthood. The NHS has also sine 1993 recognised and endorsed that dietary treatment is for life. PKU is not cured once a person turns 18. The draft guidance does not stipulate or consider the impact on a patient taking Kuvan in childhood and then having it withdrawn on their 18th birthday. These 18-year-olds are often at a crossroads in their lives at this point, for example going to university or leaving home. Managing phenylalanine levels with dietary treatment alone is very difficult, especially for teenagers. 18-year-olds accustomed to a relaxed diet through using Kuvan would not have the coping skills and tools to switch to an extremely restricted diet and would go on to suffer a whole host of issues and symptoms. This issue has been completely ignored in the guidance. This drug is used amongst adults in over 50 countries, including in Romania and Syria. But not in the UK. That fact alone is absolutely staggering.	No	
345					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment,	Wow! I can't believe you are asking this when you are literally discriminating on the grounds of both age and pregnancy/maternity! It seems entirely unlawful.	No	

					pregnancy and maternity?			
346	recommendations	1 Recommendations	they are under 18	Kuvan should be approved for all age groups. It should not be limited to just those under 18. This guidance underestimates the benefits of Kuvan treatment for adults with PKU. It says there is no risk of permanent brain damage after the age of 18, but this is directly contradicted by the statement that the brain continues to develop up until the age of 25. More recent evidence shows that brain development continues to develop well into old age. Many adults with PKU have very serious symptoms – such as depression, anxiety, brain fog and memory loss - caused by high phenylalanine levels. Protein allowance does not typically increase as patients get older and therefore dietary treatment and management only gets more difficult in adulthood. The NHS has also sine 1993 recognised and endorsed that dietary treatment is for life. PKU is not cured once a person turns 18. The draft guidance does not stipulate or consider the impact on a patient taking Kuvan in childhood and then having it withdrawn on their 18th birthday. These 18-year-olds are often at a crossroads in their lives at this point, for example going to university or leaving home. Managing phenylalanine levels with dietary treatment alone is very difficult, especially for teenagers. 18-year-olds accustomed to a relaxed diet through using Kuvan would not have the coping skills and tools to switch to an extremely restricted diet and would go on to suffer a whole host of issues and symptoms. This issue has been completely ignored in the guidance.			No	
347	recommendations	1 Recommendations	a dose of up to 10 mg/kg is used	Guidance says “a dose of up to 10 mg/kg is used”. This cap should not be in place. Clinicians should have the flexibility to prescribe the dosage according to individual patient needs and in line with the manufacturers authorisation which ranges from 5mg/kg to 20mg/kg. With this current guidance, there is a large risk that many patients would be classified as non-responders, when they in fact need the higher dose of 20mg/kg. This is the common practice in other countries. The costing against 10mg/kg is appropriate as that is likely to be the average dose, but clinicians need the flexibility to prescribe up to 20mg/kg where required.			No	
348	recommendations	1 Recommendations	The dose of sapropterin is based on weight so costs are higher for adults than children but there is no extra increase in quality of life for adults to offset these costs	My friend's child has PKU. What I cannot fathom is how my friend would tell his son that on his 18th birthday, his supply of this life changing drug and his whole way of eating and living will be taken away from him? My friend must explain that the medical recommendation is that he must stay on diet for life (the NHS has stated that the PKU diet should be for life since 1993), but at the same time it is not thought he would gain any benefit by continuing to take Kuvan. Both these positions cannot be true (especially when Kuvan is proven to show benefit for adults). It is either treatment for life or not. At the age of 18, my friend son will likely be just about to take his A level examinations, and preparing to move away to university, enjoying all the freedoms (and risks) that late adolescence brings. How can he be expected to reach his potential whilst coming off a drug that not only increases dietary options, but also improves concentration, working memory, retention, mood and anxiety levels? How can I justify to my son that in the middle of the most important examinations of his life, he must risk severe cognitive effects, even if he manages to stick to the diet. How does my friend explain to his son that while he is attempting to manage his new found brain damage, his exams, and all the other challenges of late adolescence, he must also learn how to cook ultra low protein food, stop eating most of his favourite foods and become involved in the complex process of ordering and managing prescription foods for himself?			No	
349	recommendations	1 Recommendations	There is also no risk of irreversible brain damage in adults with PKU	However, your guidance also states that brain development continues up until the age of 25. Which is it NICE? Very contradictory.			No	
350					Has all of the relevant evidence been taken into account?	No not at all regarding adults with PKU. It is clear that using lack of evidence is an excuse for not prescribing this treatment that is available around the world and is clearly effective in reducing Phe levels in children and adults.	No	

351					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	No as cost effectiveness has not been taken into account for adults with PKU and quality of life has not been considered for this patient group.	No	
352					Are the recommendations sound and a suitable basis for guidance to the NHS?	No not at all.	No	
353					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	This recommendation is discriminatory to all adults with PKU.	No	
354	recommendations	1 Recommendations	When taking into account the clinical evidence and benefits that were not captured in the cost-effectiveness estimates for children, sapropterin is considered an appropriate use of NHS resources. So, it is recommended for treating PKU in children at a dose of up to 10 mg/kg.	Talk to adults with PKU and parents of children with PKU. Gather the evidence to show cost-effectiveness. Restricting the drug dose and to only offer it to children is inhumane.			No	
355	recommendations	1 Recommendations	they are under 18	This is discriminatory. Why limit this drug to under 18s. How is this going to work once the child gets to 18. They will have to learn how to live on a more restricted diet. This will place a huge burden on the child, the parents and the NHS. It will cause more problems in the long term. Such a crucial time in a child's life to have to return to the low protein diet following a more liberal one with Kuvan. And what about the adults with PKU. Why are they being ignored? They, more than the children, need access to this drug. Not everyone will respond so the drug should be prescribed to ALL people with PKU that respond. Are there any other drugs for a condition that are stopped at 18?			No	
356	recommendations	1 Recommendations	a dose of up to 10 mg/kg is used	Why limit the amount of the dose? The dose will be individual to the patient and therefore variable. This is discriminatory and adds another level of restriction.			No	
357	recommendations	1 Recommendations	affects brain function in adults.	Therefore access to Kuvan is essential for adults too.			No	

358	recommendations	1 Recommendations	only treatment for PKU is a diet to manage phenylalanine and overall protein intake (protein-restricted diet). Sapropterin is used alongside this diet. The aim of treatment is to reduce blood phenylalanine levels and allow a less restricted diet.	Patients with PKU have only had access to a protein restricted diet since PKU was first discovered and screened for by the NHS. Why screen for a condition if you are not going to offer the drugs to treat it when they become available? Other conditions have many drug options but not PKU. The diet is incredibly difficult for the child and parents. The impact of a protein restricted artificial diet has an impact on all aspects of the child's health, mental and physical. The amino acids supplements that people with PKU have to consume, in my daughters case four times a day, are less efficient in the body than proteins contained in natural food as they are absorbed in a non-physiological way. My daughter has had so many other heath issues that stem from her artificial PKU diet: - fibrosing alopecia, irregular periods, stunted growth, anxiety, problems with slow processing speed, muscle pain, stomach pain and gastrointestinal issues. The list goes on. If she was a Kuvan responder and she was able to access these drugs her health quality of life would improve dramatically. For her it is not just about having more dietary freedom it is all the other problems she has had to face as a teenager as well as her PKU. It is not fair to put a child through all of this. The impact on her, us as a family and the cost to the NHS for all her appointments with additional specialist care and drugs must definitely outweigh the cost of prescribing Kuvan.			No		
359	recommendations	1 Recommendations	Clinical trial evidence compares sapropterin alongside a protein-restricted diet with diet alone. It shows that sapropterin effectively reduces blood phenylalanine levels in people with PKU. It is uncertain how well it works because there is only short-term clinical trial evidence. There is no clinical trial or registry evidence to show whether sapropterin reduces the need for a protein-restricted diet or how it affects quality of life.	This paragraph is contradictory - first it says "sapropterin effectively reduces blood phenylalanine levels" then it says "there is ... no evidence to show whether sapropterin reduces the need for a protein-restricted diet" Sapropterin IS effective therefore it WILL reduce the need for a protein-restriced diet!			No	
360	recommendations	1 Recommendations	It shows that sapropterin effectively reduces blood phenylalanine levels in people with PKU.	It shows that Kuvan DOES work in reducing blood Phe levels.			No	
361	recommendations	1 Recommendations	There is no clinical trial or registry evidence to show whether sapropterin reduces the need for a protein-restricted diet or how it affects quality of life.	Clinical evidence is not available because PKU is a rare disease and evidence is hard to gather from a drug that not all people with PKU will respond to and from a drug that is currently not available in the UK! Look at the evidence from other European countries and worldwide where Kuvan is routinely prescribed. I know from anecdotal evidence from the few people I have met who are "on" kuvan and the fantastic difference it has made to their quality of life.			No	
362	recommendations	1 Recommendations	The dose of sapropterin is based on weight so costs are higher for adults than children but there is no extra increase in quality of life for adults to offset these costs.	HOW CAN YOU SAY THIS??? Have you lived the life of an adult with PKU??? This is an outrageous and insulting comment.			No	
363	recommendations	1 Recommendations	There is also no risk of irreversible brain damage in adults with PKU.	But there is risk of impaired cognitive function and an increase in white matter on the brain. Look at the publication from the NSPKU "Patient Voices" and read the impact that PKU has had on quality of life. Once again adults with PKU being disregarded. Is it ok for an adult to suffer all of these mental health issues if they can't adhere to the ridiculously difficult low protein diet? Other treatment options must be made available for these people.			No	

364	recommendations	1 Recommendations	Also, there is not enough evidence on how sapropterin might be used to prevent harm to the unborn child in women with PKU who are pregnant or trying to conceive.	Once again this is outrageous and insulting to women with PKU. There is not enough evidence because it is not prescribed!! Prescribe the drug and gather the evidence for this. Women with PKU are frightened of having a baby because of the extra dietary burden on them during pregnancy and the risk of harm to their unborn child. Imagine living with being frightened about having a baby, this should be a joyous time and it is not for so many women with PKU. Some deliberately choose not to conceive because of their fear. Kuvan, for some women, would take this fear away.			No	
365	information-about-sapropterin	Marketing authorisation indication	'for the treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of all ages with phenylketonuria (PKU) who have been shown to be responsive to such treatment'.	Marketing from the manufacturer "in adults and paediatric patients" not just children! Do other countries only prescribe to children?			No	
366	committee-discussion	Recommending sapropterin for certain groups of adults cannot be justified given the cost-effectiveness estimates	Recommending sapropterin for certain groups of adults cannot be justified given the cost-effectiveness estimates	Recommending Kuvan for certain groups of adults would be discriminatory.			No	
367	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	High blood concentrations of Phe are toxic for the brain and can cause irreversible damage during brain development.	There is research that shows that the brain is still developing to the age of 25 and that changes can still carry on happening into a old age.			No	

368	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	This diet should be continued as an adult.	If the recommendation is to continue the diet treatment as an adult then the drug to treat it should also be prescribed to adults.			No	
369	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	One patient expert confirmed that there are adults with PKU in the National Society for Phenylketonuria (NSPKU) who have severe symptoms and irreversible brain damage.	Older adults with PKU did not benefit from the range of low protein foods and supplements that are available to babies diagnosed now. These people really struggled to stay on the diet. Also, these people were also told to COME OFF the diet by their doctors. Some at the age of 7 years, some at the age of 12 years and some once they reached adulthood. Some of these patients are not being followed up or contacted to advise that they return to diet. Many are lost to follow up and are suffering in the community not realising it is their PKU that is causing their problems.			No	
370	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	However, adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25. In adults, high Phe concentrations can result in short-term symptoms, which are considered reversible by lowering Phe levels through diet. These include impaired executive function, reduced autonomy, impaired social maturity, difficulty forming relationships and neuropsychiatric symptoms such as depression, anxiety and inattention. Clinical experts estimated that 10% to 20% of patients	So prescribe Kuvan to adults too! How can you expect a child on Kuvan to be able to start a protein restricted diet at 18 years. How is the NHS going to manage this? How will the drs and dietitians manage the fall out of this short sighted decision. Symptoms can be reversed by diet or by prescribing Kuvan. Adults find the diet incredibly difficult to manage. Kuvan would help this for some. Children have a lot of support from parents to maintain their diet. Adults, once away from the family home, really struggle.			No	

			struggle to maintain control of blood Phe levels.					
371	committee-discussion	High blood Phe levels in pregnancy can have harmful effects on the unborn child	In pregnancy, high blood Phe levels can have harmful effects on the unborn child and lead to abnormal development. These effects include impaired growth, impaired learning ability and birth defects such as congenital heart defects. Clinical experts explained that maternal PKU syndrome can be worse than PKU itself because the unborn child is exposed to high Phe levels during a crucial phase of development.	Adult women are frightened of having children. The current NHS policy to only prescribe Kuvan to women who are already pregnant but experts say that "Dietary measures should ideally be started before conception to avoid congenital effects" This policy is woefully inadequate.			No	
372	committee-discussion	The only treatment option available for people with PKU is a self-managed protein-restricted diet	Current clinical management of PKU is through a lifelong protein-restricted diet.	Then Kuvan should be prescribed lifelong to patients that respond to it.			No	

373	committee-discussion	The only treatment option available for people with PKU is a self-managed protein-restricted diet	Clinical experts stated that 80% of people with PKU can tolerate less than 10 grams of protein per day,	My daughter has 6 grams of protein a day. She is 21 years old. This diet has had a massive impact on her mental and physical health. It is cruel and often unmanageable.			No	
374	committee-discussion	People with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet	The primary aim of clinical management and the protein-restricted diet is to prevent irreversible and reversible brain damage by keeping blood Phe concentration levels within the ranges recommended in European guidelines. However, both clinical and patient experts highlighted that people with PKU may be outside recommended Phe ranges.	A baby born without PKU would have Phe levels of around 60 but for a baby with PKU the levels on diet are aimed at 120 - 360 and for an adult 600 - for an adult this is 10 times the amount of Phe compared to a person without PKU. This fluctuating additional Phe in the blood must be having an impact on the person with PKU. Kuvan would help reduce the Phe and maintain a good level whilst allowing the person with PKU to eat more 'normal' diet.			No	
375	committee-discussion	People with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet	30% of adults have stopped their diet and the other 20% have difficulties maintaining it.	This diet is impossible for some adults with PKU.			No	
376	committee-discussion	People with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet	The committee concluded that people with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet.	Agree 100% and Kuvan would allow this for some patients.			No	

			Many adults describe the effects of high Phe levels as 'brain fog', forgetfulness, tiredness, confusion, low mood and feelings of irritability. This can affect their ability to control their diet and maintain adequate blood Phe levels. Additionally, adults with PKU may find it difficult to juggle work, studies and family commitments with controlling their diet and maintaining Phe levels. Some adults are unable to engage in full-time work because it creates a vicious cycle of less time to control diet and higher Phe levels, leading to reduced ability to focus and organise the diet. In addition, they can have a sense of being dependent on other people for support, feel socially isolated and constantly worry about maintaining their diet (see section 3.4). The committee understood that concerns about high blood Phe levels can also affect women's sexual and reproductive health and choices. In some cases, women completely forego sex because they are afraid of becoming pregnant and accidentally harming their unborn child. Mothers with PKU describe being unable to cope with the pressures of strict dietary management while caring for their child, and experiencing anxiety, depression and inability to focus as a result. PKU is also very limiting for children, who face isolation and feel restricted in their ability to join social events such as school trips, festivities, travelling, or					
377	committee-discussion	There is a need for a treatment that can reduce PKU symptoms and give people with PKU and their carers peace of mind about blood Phe levels		Has this been taken into account at all? How with all of this evidence has NICE come to it's decision not to recommend Kuvan for adults?			No		

			meals out because of their diet. Children with PKU frequently experience difficulty with focus, depression or anxiety, disordered eating, digestive problems, headaches, low mood and sadness, feeling tired all the time and being in a heightened emotional state (including aggressiveness, psychosis and paranoia) because of high Phe levels. The committee concluded that there is a need for a treatment that can reduce PKU symptoms and give people with PKU and their carers peace of mind about blood Phe levels.						
378	committee-discussion	Sapropterin is clinically appropriate and beneficial for people with PKU that responds to sapropterin	However, mutation analysis is not routine practice in the UK.	Routine mutation analysis should be available in the UK. This would not only help with Kuvan but with diet management of those who do not respond to it.			No		

			Patient experts advised that adults with PKU who have taken sapropterin report improved day-to-day functioning, particularly concentration and mood. In addition, they were able to resume other activities such as studies or work. Parents of children with PKU report similar benefits in the mood, energy, concentration and behaviour of their children. They also report large increases in natural protein consumption, with children having a wider and more socially normal diet and greater freedom to participate in social activities. In addition, sapropterin also led to health benefits in children. These included increased bodyweight and growth, improvements in gastrointestinal symptoms and fewer mouth ulcers. Carers of people with PKU reported a significant easing of burden of care. This included not needing to prepare special prescribed low phenylalanine foods and being able to delegate childcare to others for first time. Some carers reported being able to return to work or study, increase working hours, spend more time with other children, and have time for other family responsibilities. The committee concluded that sapropterin is beneficial for those people with PKU that responds to sapropterin.					
379	committee-discussion	Sapropterin is clinically appropriate and beneficial for people with PKU that responds to sapropterin		This should be enough evidence and reason to prescribe Kuvan.			No		

380	committee-discussion	The trial evidence shows sapropterin plus protein-restricted diet is clinically effective compared with protein-restricted diet	The committee agreed that this was appropriate but concluded that the available trial evidence shows that sapropterin with protein-restricted diet is clinically effective compared with protein-restricted diet.	Evidence that Kuvan is effective.			No	
381	committee-discussion	The results of the PKUDOS registry are likely to be generalisable to NHS clinical practice	Higher proportions of patients achieved target Phe levels in the younger age subgroups (under 4 and under 12) than adults (18 and over).	Clearly this is because the parents are managing the diet for the child. Adults find this diet very difficult to maintain.			No	
382	committee-discussion	The estimate of 71.2% reduction in protein-restricted diet is not evidence-based	Clinical experts highlighted that some people with PKU who take sapropterin can completely remove protein substitutes from their diet, referencing a forthcoming systematic review.	These findings should all be taken into account when deciding whether to recommend Kuvan. Some patients may not need expensive supplements and low protein foods therefore less cost to the NHS. Have all of these calculations been done? There will also be a reduction in care needed for those patients on Kuvan having a more 'normal' diet as they will inevitably not have so many other mental and physical issues.			No	
383	committee-discussion	Long-term brain damage in children is an important aspect of PKU, but there is little evidence to estimate its effect on quality of life	but there is little evidence available to estimate its effect on the quality of life of people with PKU.	PKU treated or untreated has a massive impact on the quality of life of the person with PKU and their family. It is a complex condition with so much still to learn. I feel that many Drs think that PKU is solved with the diet treatment but if you live with PKU day in and day out you will understand how PKU impacts on absolutely everything.			No	
384	committee-discussion	The model time horizon is not long enough to capture long-term brain damage and the model is not appropriate to capture the effects of PKU in pregnancy	The model time horizon is not long enough to capture long-term brain damage and the model is not appropriate to capture the effects of PKU in pregnancy	It is very apparent from reading this report that there is not enough data gathered for decisions to be made. This is not good enough. The fact that PKU is rare should not always be used for a reason to not have evidence. Gather more evidence from the people with PKU and their families then decision making will be easier.			No	

385	committee-discussion	The utility values from the time trade-off study are highly uncertain, but are the only available evidence	Quality of life was not assessed	Why not? Quality of life is often very poor for people with PKU. Assess and compile this evidence from the people living with PKU.			No	
386	committee-discussion	Higher doses than 10 mg/kg for children and 12.5 mg/kg for adults would have a significant effect on the cost effectiveness of sapropterin	the total dose and annual costs would be much higher for adults that children, over and above any difference in the dose per kg body weight.	This is obvious and should not be a reason not to prescribe it to adults.			No	
387	committee-discussion	The costs of protein-restricted diet estimated by the company are reasonable, but the cost savings with sapropterin are uncertain	The committee concluded that the cost savings related to a reduction in protein-restricted diet are uncertain.	This should be looked at again. The cost savings would be significant related to a reduction in the need for low protein foods and supplements.			No	
388	committee-discussion	The costs of long-term brain damage and damage to the unborn child in pregnancy may be substantial, but these have not been modelled	The costs of long-term brain damage and damage to the unborn child in pregnancy may be substantial, but these have not been modelled	Again this should not be a reason not to prescribe Kuvan. Talk to the families and dietitians looking after the families. Throughout this recommendation it constantly refers to lack of evidence. The evidence is there - gather it.			No	
389	committee-discussion	Sapropterin has not been shown to be cost effective in adults with PKU	Sapropterin has not been shown to be cost effective in adults with PKU	How can you make this decision? How can you quantify this? Talk to my daughter and ask her if she considers prescribing a treatment for her condition would be cost effective!			No	

390	committee-discussion	The committee is unable to consider women who are pregnant or planning to conceive separately, and welcomes further comment and evidence on this group	The committee is unable to consider women who are pregnant or planning to conceive separately, and welcomes further comment and evidence on this group	I don't think that women who are pregnant or planning to conceive should be considered separately. All adults that respond to Kuvan should be able to access this drug in the UK.			No	
391	committee-discussion	Sapropterin is not recommended in adults with PKU for treating HPA that has been shown to respond to sapropterin	Therefore, for adults sapropterin is not within what NICE considers a cost-effective use of NHS resources.	Inhumane assumption.			No	
392					Has all of the relevant evidence been taken into account?	No, I don't feel all of the relevant evidence have been taken into account.	No	
393					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	No, I don't think all of the summaries of clinical and the cost effectiveness reasonable interpretations of evidence.	No	
394					Are the recommendations sound and a suitable basis for guidance to the NHS?	No the recommendations aren't sound and a suitable basis for guidance to the NHS. I don't feel just giving children access to use Sapropterin to treat their PKU justified and ethical. This is also discrimination against adults who are aged 18 or above who aren't able to have the drug to treat their PKU. No one should be deprived of a treatment which will help manage their Phenylketonuria(PKU) on the grounds of cost effectiveness and lack of sufficient evidence.	No	
395					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment,	Yes, I don't feel that your draft decision to allow children up to the age of 18 morally correct and there is also discrimination against age. PKU is a lifelong condition to manage and control and doesn't stop at the age of 18! How is taking away a treatment at the age of 18 ethical? I also don't feel woman with PKU should be excluded from having Kuvan as treatment for their PKU due to the harmful effects of high blood phenylalanine on the unborn child and the consequences of this on the health of the newborn. Again this is discrimination and morally wrong.	No	

					pregnancy and maternity?			
396				I believe NICE should recommend the drug Sapropterin for both children and adults(18+) with PKU or to at least those with PKU (adults and children) who actually respond to Sapropterin. I therefore don't believe that you should propose to give the drug to children only or under the age of 18 years old. In my online response I've responded to some of the text of the consultation but in my comments below I will draw upon evidence(web links) I've researched to support my reasons why I feel Sapropterin should be given to adults as well. No one should be left out as PKU is a lifelong condition/disease and impacts the quality of life for both children and adults. The reasons why I feel personally NICE should consider offering Sapropterin (from the perspective of an adult with the most severe form Classical PKU) to treat PKU for both adults and children are given below: 1/ PKU is a lifelong condition which needs to be therefore managed from a child to adulthood. PKU management doesn't stop at 18. I've mostly followed a low protein restricted diet since birth(5 1/2 - 10 exchanges daily) and understand the huge demands this brings upon me and the resulting stress such as: measuring and recording daily protein allowance; taking a disgusting/unpalatable supplement 3 times a day; taking blood tests monthly; attending appointments; restricting healthy foods like grains, eggs, legumes, nuts and seeds ; managing prescriptions/deliveries for low protein products and shopping for special dietary food low in protein. If a child was to stop taking Sapropterin at 18, the implications for returning to this sort of dietary management would be unjustifiable in terms of the detrimental affect it would have on their mental and physical well-being as well as the increased risk of other comorbidities. It would also be psychologically traumatic for them. 2/ Everyone with PKU have the right to have access to pharmaceutical drugs such as Sapropterin. No adult should be excluded on the basis of false information or lack of data/evidence which is evident in the consultation. This is unethical! 3/ I feel there is a risk of irreversible brain damage in people with PKU because evidence has shown there are white matter and grey matter abnormalities (increased white matter/decreased grey matter) when brains were analysed for people with PKU and without. Early research has shown that these changes in the brain could be linked to impaired executive functioning and slow information processing speed in people with PKU. I have suffered from both of these symptoms as of result of high phenylalanine levels (please see the document PKU and the Brain (2012) here: https://www.npkua.org/What-is-PKU/PKU-and-the-Brain(p.14-15) and watch this 20 minute YouTube video: https://www.youtube.com/watch?v=r-6V5xfqQa4. Another useful article looking into white matter damage in PKU can be found here: https://pubmed.ncbi.nlm.nih.gov/30367646. Furthermore I have not read/seen any evidence to say that this brain damage is not reversible if phenylalanine levels have been reduced. With my history of not being able to maintain consistent phenylalanine levels within the recommended range of under 600 umol/L I am at great risk of developing irreversible brain damage. There is also evidence that brains don't fully develop until we reach the age of 25 if not the 30's: https://www.dailymail.co.uk/sciencetech/article-4055490/You-think-grown-18-brains-don-t-fully-mature-hit-30.html. In the consultation you contradict yourself so it's not clear what you believe. 4/ Sapropterin treatment for adults could be life changing and would improve the quality of life for many adults with PKU. It would mean adults like myself would not be relying heavily on a highly restricted low protein diet thus reducing suffering to a great deal. An adult could eat a much more varied and healthier diet such as eggs, fish, nuts, legumes, dairy etc. This would improve physical, mental and emotional well-being. I've always struggled to lose weight due to adhering to the low protein restricted diet which is based heavily on carbs as protein source such as potatoes and high in calories due to taking daily a vitamin, mineral and amino acid supplement in addition to the calories consumed through diet. If Sapropterin was available for adults then losing weight would be an easier task as I would less reliant upon carb based foods as a source of natural protein like rice. 5/ I've haven't always maintained a very restricted low protein diet as an adult due to the demands			No	

				this brings(see earlier) and therefore I have suffered many times from high phenylalanine symptoms such as fatigue; headaches; low mood(anxiety and depression); eczema; tremors; poor focus; cognitive impairment(executive functioning)and low energy levels. This is obviously not to my wishes/liking however unlike when you are child adulthood brings more responsibility such as working; paying your bills; managing your finances; owning a car etc. I can remember working in a past job and I wasn't able to perform to the best of my ability due to experiencing these high phenylalanine symptoms. This affected my overall mental and physical well- being and of course my job. Sapropterin is needed for adults to prevent/reduce this impact high phenylalanine levels can have upon these kinds of responsibilities such as working therefore an improved quality of life. When you are an adult controlling your dietary phenylalanine daily, this can be very challenging and stressful at times since you have to juggle several commitments and responsibilities at the same time. The ability to multi-task becomes problematic if your phenylalanine levels are high as I hope you can understand. I feel the need for some pharmaceutical drug to enable me to reach my full potential as diet alone isn't enough unfortunately. It never has been. 6/ As I've had experience with not complying or adhering to the low protein diet due to the huge demands it puts upon me there has been the additional worry that this could result in nutritional deficiencies, inadequate nutrition and a risk of related health issues due to the build-up of high phenylalanine in the blood. High phenylalanine levels need to be taken into account when approving Sapropterin for adults because they really can impact the quality of life for adults and children. On the reverse, following a very restricted low protein diet has been very stressful for me and this stress coupled with often high phenylalanine levels above 600 umol/L could have caused my autoimmune disease called Alopecia Universalis(no hair on scalp or body). Alopecia has been also documented as one of the comorbidities you are at a greater risk of getting due to having PKU. https://pubmed.ncbi.nlm.nih.gov/30266197/(2018) 7/ PKU have also had an affect on my family. I would like NICE to consider this when deciding on whether to approve Sapropterin for adults. This is because as a child growing up with PKU my parents helped to support me with following the low protein diet. My mother would record my daily protein allowance which was about 6 exchanges. She would also cook foods I could have and avoid foods I couldn't like fish, meat, eggs or anything high in protein. Eating out in restaurants was always stressful and difficult due to having to make special provisions surrounding what foods I could eat. I can remember I always had chips and salad as it was the most convenient option but not necessary the most appetizing. As a child I was also very shy about explaining that I had PKU and often would socially distance myself from my colleagues at lunchtime due to feeling unable to explain to them I had PKU. With no other treatment except adhering to a highly restricted low protein diet growing up around other people/socialising became very difficult. In my adulthood and with my brain still developing there was always that worry of a risk of irreversible brain damage if I didn't maintain the low protein diet. At this stage however I became more knowledgeable surrounding PKU and its impact upon me. I cooked my own food, managed prescriptions by myself, shopped for food and recorded my daily protein allowance without the support from my family. However the impact PKU has upon me to this day is no different to me than as a child in terms of getting high phenylalanine symptoms(neurological) affecting me such as low mood, cognitive impairment(executive functioning), headaches, anxiety , tremors, eczema and tiredness. I really hope you consider Sapropterin for adults as another treatment option. 8/ I feel that all groups of adults with PKU should be given treatment with Sapropterin if they respond which includes pregnant woman and those who have extra problems managing their PKU due to their situation such as people who have a learning disability, sensory impairment, cognitive impairment, autistic and people at risk of comorbidities such as diabetes. Everyone in these groups deserve treatment with Sapropterin and there should be no discrimination or anyone excluded. To be one of the very few countries in Europe to not have Sapropterin made available for everyone is utterly appalling. 9/ Dietary treatment isn't the only factor which determines the blood phenylalanine levels of someone with PKU. Other factors such as stress, getting an infection; picking up a virus, vaccination, amount of exercise and amount of calories all affect blood phenylalanine levels. The need for another treatment in addition to a low protein diet is highly important as someone with good dietary control keeping very strict to their daily phenylalanine allowance could have a level above the recommended range of 600umol/L and suffer high phenylalanine symptoms which could eventually lead to poor health outcomes. This happened to me in January of this year when I had been very strict keeping to under 10 exchanges but my phenylalanine level was above the recommended range of 600umol/L. It was 640umol/L. This could have been caused by the Covid-19 vaccine I had shortly prior to the blood test. https://www.sciencedirect.com/science/article/pii/S1096719213003119 10/ In addition to the above reasons I would like to include my YouTube video to further support my		

				response to this consultation. Please find a link to this here: https://www.youtube.com/watch?v=P9ftDhyZYPw					
397	recommendations	1 Recommendations	there is no extra increase in quality of life for adults to offset these costs. There is also no risk of irreversible brain damage in adults with PKU. This means the cost-effectiveness estimates are higher than what NICE considers an acceptable use of NHS resources.	I disagree with all of these statements. There is an improved quality of life with Sapropterin as blood phenylalanine levels would be lower (if responder) leading to a reduced risk of high phenylalanine symptoms such as poor focus, brain fog, fatigue, low mood or cognitive impairment. There is also a risk of irreversible brain damage in adults with PKU because brain development doesn't stop until the age of 25 therefore high blood phenylalanine levels can enter the brain and cause white matter and grey matter abnormalities(research evidence shown this). I therefore conclude the cost-effectiveness estimates are not higher than what NICE considers an acceptable use of NHS resources.			No	

398	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	Clinical experts explained that brain development peaks at around age 12. After this high Phe levels are unlikely to affect IQ. However, adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25.	You have contradicted yourself because earlier you were incorrect in saying that there is no risk of irreversible brain damage with adults who have PKU and here you say there "may still be a risk of long-term brain damage". I believe there is a risk of irreversible brain damage in adults with PKU who can not control their phenylalanine levels through diet. Evidence has shown white matter and grey matter abnormalities in the brain with high phenylalanine levels. Even with adhering to a low protein diet there is still a risk of irreversible brain damage because other factors like stress, infection, low calories can all affect the level of blood phenylalanine. As you rightly said brain development continues after you have reached the age of 18 therefore the risk of brain damage is just as great if you are an adult than if you were a child under 18. Sapropterin must be given to adults therefore to reduce this risk and to avoid brain damage in adults.			No	
399	committee-discussion	Long-term brain damage in children is an important aspect of PKU, but there is little evidence to estimate its effect on quality of life	but there is little evidence available to estimate its effect on the quality of life of people with PKU.	I disagree that there is little evidence to estimate long term brain damage effect on the quality of life for children because by looking at the evidence which surrounds the fact white matter and grey matter abnormalities occur when phenylalanine levels are high one can estimate or understand the impact this has on people with PKU. This is because these abnormalities affect brain function, mood and energy. When these have been affected this affects the quality of life for PKU people.			No	
400	committee-discussion	The costs of protein-restricted diet estimated by the company are reasonable, but the cost savings with sapropterin are uncertain	The committee concluded that the cost savings related to a reduction in protein-restricted diet are uncertain.	I don't believe this is correct. Not everyone with PKU will respond to Sapropterin. So the costs predicted may not represent the right amount. Allowing Sapropterin for adults would reduce the costs of a low protein diet (supplements and low protein diets) and therefore would cancel out the cost for Sapropterin. It would be cost effective because not everyone will respond to the drug, only a small percentage of people with PKU. Maybe a test can be carried out to see who with PKU responds to Sapropterin then accurate costs for the drug could be calculated?			No	
401	committee-discussion	A 10 mg/kg dose in children and 12.5 mg/kg in adults, and a 71.2% reduction in protein-restricted diet is acceptable	ERG's model focuses on the main drivers of cost effectiveness: reduction in protein-restricted diet, cost of sapropterin treatment and quality of life benefits because of better Phe level control and reduced need for a protein-restricted diet.	I think these need to be more reinforced and looked into more deeply with a greater understanding and appreciation for someone who has PKU and the impact these would have on their quality of life. Saproterin would help alleviate a lot of suffering for adults with PKU and improve their quality of life,			No	

402	committee-discussion	Sapropterin has not been shown to be cost effective in adults with PKU	but there are no corresponding increases in quality of life to offset these costs. Also, the additional consideration of the risk of irreversible brain damage did not apply to the adult population.	This is absolutely false. You need to look earlier in your appraisal as you have contradicted yourself. Evidence has shown that there is risk of irreversible brain damage in adults with PKU due to white matter and grey matter abnormalities shown in brain scans and brain development does not stop until you reach the age of 25. You cannot conclude Sapropterin not to be cost effective for adults with PKU on the basis of false information and misinterpretation of the clear facts.			No	
403				The intention for continuation of Sapropterin for children that will be treated and then turn 18 should be outlined in the document. I would hope that the provision that was made in Australia when they introduced sapropterin for under 18s would be written into NICE recommendations. That is that if a child is treated with the drug throughout their childhood, it would need to be continued into adulthood and it wouldn't be stopped at 18. Nothing that this age is crucial for many young lives as they go to uni or the workforce. It would be detrimental to these young adults to expect that they could stop the treatment and revert to a full pku diet.			No	
404					Has all of the relevant evidence been taken into account?	No - see my response under 'Recommendations'	No	
405					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	No - see my response under 'Recommendations'	No	
406					Are the recommendations sound and a suitable basis for guidance to the NHS?	No - see my response under 'Recommendations'	No	
407					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	Yes, and you have not taken them into particular consideration. See my response under 'Recommendations'	No	

				I welcome the recommendation that children will be able to access Kuvan via the NHS but I believe that all patients of all ages with PKU who respond to Kuvan should be able to use this medicine on the NHS. The Appraisal Consultation Document issued in February 2021 does not take into account a number of important issues regarding treatment with Kuvan, PKU itself, and the current 'diet only' treatment. NICE has most definitely not taken into account all relevant evidence, especially that of PKU patients themselves. It has also seemingly ignored a large body of scientific evidence about PKU patients and their experiences, particularly that presented at earlier stages by the National Society for PKU. The recommendations are not sound and are in no way a suitable basis for guidance to the NHS and I believe NICE has most certainly not made sure that it avoids unlawful discrimination. My response should be understood as a 38-year-old educated to doctoral level with classic PKU, whose diet comprises 9g protein per day. I therefore have 38 years of lived experience being treated with the diet primarily by my family as a child and then self-administering it as an adult. Proposal to cease treatment with Kuvan When Patients Turn 18 NICE has in no way considered the problem of young people stopping treatment with Kuvan on their 18th birthday. Managing phenylalanine levels with dietary treatment alone is very difficult. It is dependent on having parents who administer the diet correctly when the patient is a child, as mine did for me, and learning the diet from them, with the support of clinicians who can advise from afar. NICE has not taken into consideration that children who have been on Kuvan since infancy will not have learnt the skills to self-administer the diet to the same degree as someone treated by diet alone during infancy, nor will their parents have learnt these skills, meaning they will not have an important source of support and understanding of the diet and its difficulties. NICE has also not taken into account that all those skills will have to be introduced at age 18 and will be an incredible – and probably impossible – burden for most if not all 18 year olds to take on, especially at a time when teenagers are leaving home, starting work, and establishing themselves as adults in the world. Quite simply, young people used to a relaxed diet through using KUVAN will not have the coping skills to switch to a strict diet which involves doing for themselves what my parents did for me as a child and what I do for myself now having learnt from them. This includes but is not limited to: • constant shopping for and preparation of suitable meals • precise measurement of all foods and drinks such as milk • planning one's life around food – ensuring you have enough low-protein food when you go out, negotiating eating safely and according to the diet at a place of education or work, and in social settings where you are not in control of what food is being offered • constant management of prescriptions - which are often not filled correctly by GPs and not necessarily ordered correctly by pharmacists (see Ford S, O'Driscoll M, MacDonald A.Prescribing issues experienced by people living with phenylketonuria in the UK. Molecular Genetics and Metabolism Reports 2019: 21 100527) • regular self-administrated blood tests, at least monthly and several times a week for women on pre-conception diet – and it is worth remembering here there is still no home-testing kit that is available to people with PKU so they can monitor levels in real time • attending regular hospital appointments and staying in touch with dieticians to modify the diet if high phe levels are found • constantly having to explain the diet to friends, co-workers, serving staff, and medical professionals who know less about it than you as the expert patient • constantly advocating for yourself, especially to medical professionals when prescriptions are refused or messed up, and also to hospitality staff, who sometimes can be extremely hostile or uninterested in accommodating the PKU diet • explaining the diet, and the implications for women in relation to Maternal PKU Syndrome, to people (including, as adults, new partners) which is emotionally exhausting • advocating for yourself to bodies like NICE, which is especially tiring when evidence already available in the public domain has clearly not been understood or considered properly As this list indicates, NICE has also not taken into consideration the emotional burden of the diet for all PKU patients. My life is shaped around my diet, and there is no other option. It takes up so much time and causes me so much anxiety, robs me of so much spontaneity in life, and has meant that I have not done what I would really like to do in life. I constantly have to think about what I have eaten and what I will eat, all day, every day, and plan my life accordingly. I have to make sure that if I go out			
408	recommendations						No	

I have things I can eat and my protein substitute, because I cannot rely on suitable food being available around me, or what happens if I get delayed and don't have anything with me, or if plans change suddenly. 80% of supermarket food is not suitable for people with PKU, and I often struggle to find suitable things beyond fruit and crisps if I am out and have not brought lunch with me. This is especially a struggle when I am travelling for meetings as part of my job, and the unpredictability of meeting times and lengths can have effects on my phe levels if I do not have food immediately to hand. If I do go out to eat at a restaurant I have to ensure there is something I can eat, which curtails my social life and means I am constantly revealing and explaining my health status to co-workers, friends, and dates – and usually the only thing on the menu that I can eat is chips and salad or vegetables, because everything else is meat-based or either vegetarian and made with cheese and pastry or vegan and includes pulses, nuts, and tofu. Eating out often another source of anxiety rather than a treat or a pleasure; most recipe books and cooking programmes are largely full of things I cannot make. The PKU diet makes me feel socially isolated from my peers and from the rest of society, and has a negative impact on my life day to day.

It is exhausting to manage the diet constantly, and build my work, hobbies, and relationships around it so that I can continue to live independently, carry on having a good job, and have friendships and relationships. The diet also means that I have to plan holidays like military operations to ensure that I have all my low protein foods and protein substitutes, which run into the kilograms in weight for even just a couple of weeks away , and that the country I am going to will have a cuisine that includes things I can buy and eat easily – and even then it is difficult to explain the diet. I have sat in a restaurant in Athens in 2018 and been refused service when I was really hungry because I could only eat a couple of side dishes and they wouldn't let me stay unless I ordered a main course, none of which I could have. By the end of the night I was in tears. I have sat in a pub with my entire department at work when we were having Christmas Dinner in 2019 and watched them eat their main course when I didn't have anything because the person taking the booking didn't pass on the message that I had special dietary requirements so they didn't have anything I could eat. I was eventually presented with a plate of white rice and broccoli. I've always wanted to go backpacking and travel the world, including Asia and Africa, potentially working abroad as a journalist covering conflicts – but I can't travel spontaneously when I have to take kilograms worth of protein substitutes and low-protein food with me, and measure my food precisely every day, and can't be posted anywhere where supplies would be unreliable. PKU robs me of many joys others take for granted in life. I have a PhD but it took me an extra year, which my GP signed off because of my anxiety, which was caused by trying to manage my diet and such a significant project as a thesis, as well as just try to live and grow as a young person. I have cried in front of my GP years later after reading the NSPKU's Survey Results, which I took part in and which have now been translated into two important studies that show just how difficult PKU and the diet is for many patients (Ford S, O'Driscoll M, MacDonald A. Living with Phenylketonuria: Lessons from the PKU community.
Molecular Genetic and Metabolism Reports 2018; 17:57-63 and Ford S, O'Driscoll M, MacDonald A. Reproductive Experience of Women living with PKU; Molecular Genetics and Metabolism Reports 17 (2018) 64–68). I am not alone in my experiences of constant high anxiety and finding the diet difficult and something that life has to revolve around. The results of the NSPKU's survey make clear the extremely difficult burden the diet is and the significant impact it has on adults' lives and NICE does not appear to have taken this evidence into account at all.

The time and energy I have to put into my diet and the way it curtails what I can do in life on micro and macro level means that I simply cannot contemplate a more high-powered career, earning more money and paying more in tax. If all PKU patients who responded to it had Kuvan throughout life, they would potentially be able to contribute more economically and socially to this country. NICE has ignored this in its modelling.

NICE has also not taken into consideration the fact that children used to Kuvan would not have grown up being used to the low-protein food that comprises a significant portion of the PKU diet treatment, nor the protein substitutes that are essential to the diet. The low-protein foods are often high in carbohydrates and sugar, bland, and difficult to cook with. The protein substitute (across brands and forms) is extremely unpalatable (it often makes me retch, and I have been known to throw up taking it), it makes breath smell, and its acidity, combined with the amount of sugar I necessarily have to have in my diet is, I believe, probably a significant contributing factor to the numerous dental fillings and two crowns I already have. Many people with PKU report similar dental issues – which of course cost the patient (if private) or the NHS money to rectify. NICE has not taken this into account in its economic analysis either.

To assume that 18 year olds would move onto this highly restrictive diet which is so unpalatable and curtails the amount of natural protein that can be eaten in comparison to being on Kuvan, as well as the extremely significant way in which the diet curtails a PKU patient's life, is utterly ignorant of what the diet is really like. This diet is not like Weight Watchers –it excludes around 85% of foods, it is for life, it is not optional, and the alternative is that the young person ends up with high phe levels and the numerous significant symptoms that come with them. Stopping Kuvan at 18 years old will mean that lots of young people who will potentially be able to contribute to society in the ways they would otherwise be able to – including economically – and will simply do not follow any treatment for PKU and not fulfil their potential. They will also be left struggling with all the difficulties and curtailment of life that high phe levels and their symptoms entail. NICE has not factored into their analysis this loss of potential, and the cost of the NHS treating the young people who will have had Kuvan taken away from them.

NICE's Undervaluation of Adults Being Treated with Kuvan

NICE's analysis underestimates the benefits of Kuvan treatment for adults with PKU. I find it particularly worrying that NICE suggests stopping Kuvan at the age of 18 in its draft guidance but then on p. 6 of the document states that 'brain development does not stop until about age 25'. This contradictory statement is illustrative of the extremely misguided understanding of PKU and quite frankly the poor logic of the whole appraisal consultation document. It also does not take into account that neuroscience is showing that the adult brain continues to change and develop throughout life, including throughout adulthood, through structural and functional neuroplasticity and also neurogenesis. There is good evidence that many adults with PKU have very serious symptoms caused by high phenylalanine levels in adulthood: see, for example, the quotes from and results of the survey discussed in Ford S, O'Driscoll M, MacDonald A. Living with Phenylketonuria: Lessons from the PKU community. Molecular Genetic and Metabolism Reports 2018; 17:57-63. These include brain fog, depression and poor memory, all of which I have experienced even when on diet as my phe levels can fluctuate due to illness, my menstrual cycle, or simply mis-calculating or being given the wrong food or drink and inadvertently having it (mostly instances where I have been given a drink which I have later found out had aspartame in it). I also experience anger, slow speech, and even more anxiety than usual when I have high phe levels, and this is noticeable in my job which includes a lot of discussions with colleagues and external people. These symptoms affect my work, my personal relationships, and my enjoyment of life and negatively impact me. Kuvan is routinely prescribed for adults in other countries so clearly health authorities in those countries recognise that Kuvan improves the medical outcomes and quality of life of patients, therefore I suggest that NICE has not taken into account the relevant evidence from those other countries, which include numerous studies that will not doubt have been cited by other respondents to this consultation including the NSPKU.

For me as a person with PKU and one who has been on diet for life, Kuvan would be transformative if I responded to it. It would mean I could live a much freer and happier life, including not having to worry about my phe levels all the time and the symptoms of high levels, and so having more time to devote to work and family life, progressing my career and being more relaxed and happier as a friend, daughter, co-worker, and partner. It would mean being able to eat more natural protein and so being healthier in my body as well as my mind, knowing I was giving my body all the natural nutrients it needs especially going into middle age; being able to eat out and socialise more like everyone else, enjoying food more and being able to eat different foods, and being freer to travel and enjoying going to parts of the world that would otherwise not be possible due to the difficulties of relying on all my prescriptions and a cuisine that had enough free foods for me to get by and a culture accommodating of the modifications I need to many dishes to make them compatible.

NICE has also ignored the fact that many adults with PKU simply cannot cope with dietary treatment. The NHS should not leave people without a realistic option for treatment. In particular, many adults who experience difficulties were told by the NHS when they were children in the 1970s-1990s that they did not need to continue the diet in their late teenage years and in adulthood, and so didn't. I thank God I am not one of them and that when given the option to 'relax' the diet at age 16 I did not, as I believe I would not have the job and life I have managed to get without strictly adhering to the diet as an adult. The NICE draft guidance does take into account that patients in the 1970s-1990s were advised in this way, and that Kuvan would help them control their phenylalanine levels in a way they cannot manage on their own. Currently, the draft guidelines as a whole are unethical, for all the reasons stated above and below and more; to ignore the way these adult patients have been advised and treated in the past, and who have followed medical advice given to them that has impacted so negatively on their lives meaning they constantly struggle with high phe levels, would be especially

unethical. Concomitantly, those like me who spend an enormous amount of time and energy at the expense of other areas of their lives on adhering to the diet because they always have done and need to keep it up should not be penalised by being restricted access to Kuvan or any other future treatments for PKU. NICE and the NHS should be prioritising funding for treatment to those of us who have health conditions that we have through no fault of our own, and which cannot be cured, unlike, for example, Type 2 Diabetes, which can be reversed through recourse to a diet, exercise, and healthy lifestyle.

NICE's Comments Regarding Women with PKU and Maternal PKU Syndrome; Pregnancy and Maternity Discrimination in NICE's Recommendations

NICE has not considered fully the harm of Maternal PKU Syndrome to the woman with PKU as well as to any unborn child. Worry about the potential of Maternal PKU Syndrome is significant for many women with PKU and lasts throughout the life period during which it is possible to get pregnant, from puberty until the menopause (childbearing years are not just 18-40, despite what NICE's draft guidance states on p. 25 at 3.24!). When deciding that Kuvan is not cost effective in adults, NICE has ignored the benefits to women with PKU of using Kuvan to help them have happy intimate relationships without having to worry about an unplanned pregnancy resulting in Maternal PKU Syndrome, and have safe and happy pregnancies, whether planned or not. This last point is significant, as no woman with PKU should have to go through life thinking she must only have a planned pregnancy or face the dire consequences for the unborn child and sense of personal guilt that comes with an unplanned PKU pregnancy. This worry is real and constant. It has affected my own life significantly. I grew up from the age of 12 being told about the negative consequences of Maternal PKU Syndrome by clinicians and it terrified me so much I have been unable to form healthy intimate relationships until well into my 30s. This was only when I realised - through the NSPKU's Survey Results (see Ford S, O'Driscoll M, MacDonald A.
Reproductive Experience of Women living with PKU; Molecular Genetics and Metabolism Reports 17 (2018) 64–68) - that I was not the only person that thought and felt this way, which I had always been extremely ashamed of and couldn't speak about, and thought that it was because something was pathologically wrong with me. Rather, this is of course an unsurprising reaction to being told from childhood that I could be responsible for a child having physical deformities and learning disabilities, and taking this heavy burden seriously and - at the same time - not receiving any clinical help in processing this. Having PKU as a woman has shaped my personal life beyond what most people could imagine and is directly responsible for the fact that I do not have children and may not ever have children. This is a source of deep distress to me; it has robbed me of years of happiness in personal relationships, and the NSPKU survey results and study show that I am far from alone in PKU having an extremely significant effect on my sextual and reproductive health – both physical and mental. NICE should take these survey results and the article based on them extremely seriously and I am puzzled as to why it has not already done so – the voices of women PKU patients have already spoken in a large number through that and the draft guidance appears to have ignored them. By asking for more evidence, NICE is asking women with PKU to perform difficult and significant emotional labour disclosing details of their most intimate personal life and I expect NICE's subsequent documents relating to this consultation to acknowledge this explicitly. NICE should also think carefully about what it is asking of women directly affected by PKU and, in the future, other conditions that relate to areas of psycho-sexual health and wellbeing and pregnancy, when it states that it 'welcomes comments and any further evidence'. I know of other women with PKU who have had harrowing experiences in this area, including being told to get an abortion or losing a child - NICE should be ashamed that it has ignored the published evidence of these experiences and is asking women to relieve them again because it can't be bothered to accurately analyse and include this published evidence in its draft consultation.

I would also like to note that women without PKU don't have to think about Maternal PKU Syndrome if they happen to fall pregnant without planning it, so why should women with PKU have to endure this disadvantage? Women PKU patients should be able to access Kuvan throughout their lives not just during a pre-conception period and during pregnancy. To do otherwise would discriminate particularly egregiously against women with PKU in relation to pregnancy and maternity.

NICE has recognised that controlling phe levels is important in early pregnancy, ideally before conception, and has recognised that this would reduce the risks of Maternal PKU Syndrome. However, it has not considered in its proposal to stop treatment of Kuvan at 18 about how women would be able to cope with going onto the even stricter-than-usual pre-conception diet to avoid Maternal PKU

				Syndrome. I would suggest, as someone with 38 years-experience of the PKU diet, that most women who were treated with Kuvan from infancy would find the pre-conception diet more or less impossible, and NICE has not factored into its economic modelling the costs of the NHS treating more children born with Maternal PKU Syndrome as a result. Furthermore, NICE has not included the harms from high levels in early pregnancy in the cost analysis. Nor has it taken into account the experiences of women with PKU who have gone through the pre-conception diet and a pregnancy. This is a time when hormonal changes and other health changes due to pregnancy make the diet extra difficult, and also a time which can result in severe illness that makes the diet extremely difficult both mentally and physically, potentially raising phe levels and also making the experience traumatic for the woman. It does not appear to have taken into account the costs needed to treat women with PKU during and after a pregnancy, especially one that has involved high phe levels, and the mental and physical effects that are related to this, including physical sickness necessitating hospitalisation and counselling to process trauma. The hormonal changes experienced by women during the menopause should also be taken into account by NICE, as hormonal changes in my experience contribute to fluctuating and high phe levels. I dread how the menopause may affect me after hearing the expreriences of other women with PKU in their 40s. Women need help through treatment with Kuvan to ensure they can maintain low phenylalanine levels throughout life and to help ensure they are as healthy as possible into old age. I believe that NICE has failed to take account of the issues experienced by women with PKU – whether they are at the stage in life where they want and can have child or not - and that this is a major failing in the draft guidance. NICE's Proposals in Relation to People with Disabilities People with learning disabilities are at a higher risk of being unable to control their phenylalanine levels with dietary treatment. The need for help with dietary treatment might also restrict the independence of people with learning difficulties. NICE recognised that people with learning difficulties might struggle with dietary treatment but there is no evidence that this has been included in the cost analysis. NICE's Proposed Recommendation in Relation to Kuvan Dosage NICE has recommended using KUVAN at a dose of 10mg/kg. I agree that clinicians in the UK will prescribe more efficiently than in the US and that an average dose of 10mg/kg is appropriate for the cost analysis. However, I believe that clinicians should be able to prescribe within the marketing authorisation, which ranges from 5mg/kg to 20mg/kg. Conclusion I believe that all people with PKU should have access to Kuvan on the NHS, and all future treatments for PKU that become available should also be funded to enable people with PKU to live full, happy lives, and fulfil their potential. Yours faithfully, Dr Philippa Turner				
409					Has all of the relevant evidence been taken into account?	There may be more evidence to support the use of Sapropterin for women that are planning a pregnancy or are in the early stages of pregnancy. As we are a paediatric centre, that is not our area of expertise, so are unable to comment.	Yes	Dept of Metabolic Medicine, Great Ormond Street Hospital NHS Foundation Trust

410					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	Yes. As per the comment in the main document, we agree that a reduction in amino acid supplement of 71.2% for all responsive patients may not be achievable, but we do anticipate that there will be a reduction in amino acid supplement for all responsive patients.	Yes	Dept of Metabolic Medicine, Great Ormond Street Hospital NHS Foundation Trust
411					Are the recommendations sound and a suitable basis for guidance to the NHS?	Please see comment made on the Implementation section. We request that there are clear national guidelines on the plan for implementation of Sapropterin.	Yes	Dept of Metabolic Medicine, Great Ormond Street Hospital NHS Foundation Trust
412					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	The implementation guidelines will have to be such that the process of roll out of responsiveness testing is fair. The process will be time-consuming so it will not be possible to test every patient for responsiveness immediately, a fair and gradual roll out over time will be required. We will need rely on guidance or a protocol from a higher level for support in this.	Yes	Dept of Metabolic Medicine, Great Ormond Street Hospital NHS Foundation Trust
413	committee-discussion	The sapropterin dose used in clinical practice in the UK would be lower than used in the PKUDOS registry and in line with European practice		The current summary recommendations say that a dose of up to 10mg/kg is used. We feel, given the Summary of Product Characterists (SmPC) indications, there should be flexibility around the dose (between 5 - 20mg/kg) at the discretion of the managing clinician. This would enable the clinician to decrease or on the rare occasion increase the dose based on the clinical need of the patient.			Yes	Dept of Metabolic Medicine, Great Ormond Street Hospital NHS Foundation Trust
414	committee-discussion	A 10 mg/kg dose in children and 12.5 mg/kg in adults, and a 71.2% reduction in protein-restricted diet is acceptable		We agree with the committee's conclusion that it is likely that responsive patients will reduce their amino acid supplements but we cannot be certain that it will be a reduction by as much as 71.2%. Amino acid supplements will be reduced by the maximum safe amount.			Yes	Dept of Metabolic Medicine, Great Ormond Street Hospital NHS Foundation Trust

415	implementation	4 Implementation		Patients with PKU are managed in a limited number of specialist centres. This means that although a rare condition the number of patients with PKU at any one single specialist centre is significant. Responsiveness testing and the dietary adjustments required upon starting treatment with Sapropterin will be time consuming. It will not be possible to commence everyone on treatment at once, but will need to be introduced over a timeline of several months. There will need to be clarity and detailed national guidelines on the practical implementation of Sapropterin as a treatment option. Guidance will need to include how to perform a responsiveness test, the definition of response, how to ensure the roll out of responsiveness testing is fair i.e. which patient groups should be tested first, monitoring and outcome threshold for continued use.			Yes	Dept of Metabolic Medicine, Great Ormond Street Hospital NHS Foundation Trust
416	proposed-date-for-review-of-guidance	5 Proposed date for review of guidance		Given that it is likely to take a long time to implement the new treatment would it be more appropriate to review when a target number of patients have been commenced on Sapropterin for a specified period of time?			Yes	Dept of Metabolic Medicine, Great Ormond Street Hospital NHS Foundation Trust
417					Has all of the relevant evidence been taken into account?	No. Experiences of PKU patients have not been considered. It is clear that the authors of the appraisal do not have an understanding of the impact of PKU on adults, pregnant women or children. There is considerable evidence with regards to the effects which does not appear to have been considered.	No	
418					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	No. Again, it is clear that the effects of PKU have not been understood. The impact on quality of life has been dismissed. PKU is a rare disorder meaning there is not a huge pool of patients from which to draw evidence, so complaining that evidence contains insufficient numbers is unreasonable.	No	
419					Are the recommendations sound and a suitable basis for guidance to the NHS?	No. The recommendations are contradictory in nature and do not sufficiently consider the benefits of the drug to adult PKU patients.	No	
420					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	Yes, the recommendations are clearly discriminatory on the basis of age. Adults are denied access to the drug because it might cost too much money, despite the clear evidence that the drug works and the clear evidence that adults with PKU are significantly damaged both physically and mentally by high phenylalanine levels. It is also discriminatory to pregnant women in denying the drug to them when the benefit is completely clear and there is considerable evidence of a) the effect of the drug in reducing blood phenylalanine and b) the damage caused by high phenylalanine in pregnant women	No	
421	recommendations	1 Recommendations	So, it is recommended for treating PKU in children at a dose of up to 10 mg/kg.	The recommendation for the drug to be effective is 5-20 mg. By limiting the dosage at this point, the effectiveness of the drug will be reduced. There is no medical justification to limiting the dosage to 10mg, just a decision based on money. This is failing PKU children and adults in England.			No	
422	recommendations	1 Recommendations	they are under 18	There is no part of PKU life that gets easier with age. PKU does not disappear at 18 years old (despite what I was told as a child). Managing the PKU diet becomes harder as a patient grows older and takes responsibility for a diet for themselves. A child who has had access to a drug for 18 years will have no ability to manage a diet as restrictive as the PKU diet without Kuvan. This is also discriminatory against adult PKU patients, with no reasonable medical justification other cost.			No	

423	recommendations	1 Recommendations	a dose of up to 10 mg/kg is used	This is not in keeping with the recommended and dosage and is a figure based purely on cost. This will just mean that the benefits of the drug are felt be fewer people and the treatment will be significantly less effective.			No	
424	recommendations	1 Recommendations	It is uncertain how well it works because there is only short-term clinical trial evidence.	Yet as of May 2017, "Experience with KUVAN totals more than 20,950 patient-years" - https://www.kuvan.com/hcp/about-kuvan/10-years-of-kuvan/			No	
425	recommendations	1 Recommendations	There is no clinical trial or registry evidence to show whether sapropterin reduces the need for a protein-restricted diet or how it affects quality of life.	You state "that sapropterin effectively reduces blood phenylalanine levels in people with PKU". Given that the protein-restricted diet is undertaken in order to reduce blood phenylalanine levels, clearly there would be a reduced need for a protein-restricted diet if sapropterin has already reduced blood phenylalanine levels.			No	
426	recommendations	1 Recommendations	no extra increase in quality of life for adults to offset these costs	Is the increase in quality of life not sufficient? The prevention of brain damage and removal of effects on brain function are significant increases in quality of life. This is nothing to do with care and improving the quality of life of PKU patients, it's a decision based purely on cost. Not measurement of the benefit of the treatment as clearly the actual impact of PKU has not been understood by the decision makers. If there is no risk of irreversible brain damage in adults with PKU, why is the recommendation diet for life? There is an abundance of evidence that diet must be continued for life, as the effects of PKU continue to be significant throughout the patients life, yet this report seeks to dismiss the issues PKU patients suffer in order to justify a non-sensical and purely financial decision. The cost of diet is not insignificant. Kuvan would reduce the need for low protein dietary items. The diet is unmaintainable into adult life. Without Kuvan, PKU patients will suffer the effects of not being able to manage their diet and will become increasingly reliant on the NHS to deal with the effects at significant cost.			No	
427	recommendations	1 Recommendations	There is also no risk of irreversible brain damage in adults with PKU.	Yet earlier it is stated that "raised levels of phenylalanine...affects brain function in adults" Is the suggestion that it is possible to reverse the effects?			No	
428	recommendations	1 Recommendations	There is also no risk of irreversible brain damage in adults with PKU	On what basis is this statement made? MY PKU levels were excellent throughout childhood but slipped during adulthood. I have seen clear issues with executive function, memory, concentration, understanding of complex concepts and neurological issues. These are not reversible. It was already stated previously in the document that high blood phenylalanine levels affect brain function.			No	

				This is a very short sighted view on the impact of the drug and the effects of high blood phenylalanine levels leading to increased reliance on NHS resources. As a PKU patient, I have recently had an MRI scan to identify any changes in my brain. The results showed a reduction in white matter which was explained by my PKU consultant as "expected in PKU". I am not an expert on brain function and I received no further explanation of what these changes mean, but information about the effect of white matter reduction are not at all positive. Why is this just accepted? Because adults need more Kuvan than a child? We should just accept a “reduction in brain function”? What price do you put on your “brain function”? Personally, I did not think that I had any mental "effects" from PKU up to my thirties. However, as I am now 42 I have seen that significantly change. I can also look back and see how I clearly was affected in my younger years but unable to identify it, primarily because of how PKU had affected my thinking. I have always been "on diet" but make no mistake, this is not a sustainable diet. Over the years, there are times where I have been completely unable to maintain the diet. This ties in with social changes as I grew older (going out to restaurants, pubs etc) to just plain inability to stick to such a restrictive diet, non-stop, for 42 years. I can now see the damage that those periods of being unable to maintain the diet as an adult have had. As a child, my levels were near perfect. When I was born, my parents were told they would be lucky if I was able to go to a “normal” school. That was the expectation of PKU at the time. Luckily, I was under the care of fantastic doctors and dieticians at my local hospital that went above and beyond to learn about PKU and manage my condition. Consultants from Great Ormond Street travelled over twenty miles to my local hospital for my appointments. Fantastic, caring people. My parents were told not to go and read about PKU at the library (no internet then) as it would just scare them. With no other source of information, they went to the library anyway. Stories and photos of children and adults in mental homes were what they found. My parents did absolutely everything they could to give me the best start in life and it led to my mum nearing nervous breakdown during my childhood. This was identified by my PKU dietician who again, went above and beyond to help my parents through. My parents were told I would only need to be on the diet until I was five. As I neared that age, they were told I would need to stay on the diet till I was a teenager. When I was nearly a teenager, they were told I’d need to stay on the diet until I was 18 or an adult. Then I was told I needed to be on diet for life. The majority of people are unable to stick to a pretty simple weight loss diet for more than a week. Try the PKU diet for 42 years. This doesn’t get any easier with age. It gets worse. Harder. More damaging. As a child, you eat what you are given, your parents manage your diet and you just have to suffer it. Missing out on the things your friends eat, being the one with the weird food, having to force down the supplements. Not being invited to parties because other parents are scared of what they can give you. Not being able to go on school trips because the teachers don’t understand your diet. But you don’t have responsibility for the diet. One you have responsibility for the diet, all that hard work that your parents have been doing - making multiple versions of every meal, organising huge collections from the chemists, dealing with sometimes obstructive doctors, hand making bread multiple times a week (including all the loaves that don’t turn out edible because the water was a bit too warm, or they added a bit too much salt) - that becomes your responsibility. And it’s a huge responsibility. And it’s unmaintainable. You start going to an adult PKU clinic, where the undertone is always that if you want to go off diet, then fine, give it a go. That the symptoms you are experiencing aren’t caused by PKU. It devalues your efforts. That despite being above the acceptable European range for blood phenylalanine of 300-600, you are still in the top 25% for the clinic. What does that tell you about the other 75%? Clearly struggling. I couldn’t even get life insurance because my blood phenylalanine levels were 700. And I am in the top 25%! My parents and paediatric dieticians’ efforts saw me into the top groups in my school classes, gaining entry to one of the best local secondary schools, achieving 8 GCSE grades A-C, a BTEC National Diploma Distinction in Computer Science and a BSc Honours Degree 2:1 in Software Engineering. This takes me to the age of 21. I struggled with the diet at University, I found studying for my degree particularly hard and began to notice the differences in my ability based on my PKU levels. As I became more responsible for my diet, it became more and more difficult to manage and maintain a ‘normal’ lifestyle. Socialising changed. From 18+, my friends went to pubs, restaurants etc. All very difficult to partake in and maintain ‘good’ PKU levels. I never came off diet and I still stuck to it as best I could, but at times I was less strict. I had to be. It was impossible to manage everything. Following my degree, I entered my first job developing medical systems for a local company before securing a job within the insurance sector, developing internal insurance management systems, rising to deputy IT manager before moving into consultancy for a blue chip insurance company. At this point, despite			
429	recommendations	1 Recommendations	the cost-effectiveness estimates are higher than what NICE considers an acceptable use of NHS resources			No		

being aware that I wasn't always able to maintain my diet 100%, I had been on a steep upward trajectory and felt I was able to deal with the effects of my diet. I started my own software development company at 30 and continue to run it today, developing language learning systems to teach English as a second language in developing countries.

However, over the last ten years, from my early thirties, I have started to notice issues. My memory has got progressively worse. I manage by making extensive notes so as not to forget things. I work in an environment that requires being "switched on" mentally and on multiple occasions there have been issues where I have forgotten to do something or I am asked about a piece of work that I completed but do not have any memory of. I have even completely missed meetings I have arranged. This is proving a problem and is unsustainable. I struggle to understand concepts where previously I picked things up naturally. I take much longer to do things. I am distracted. I have trouble focusing. I have discussed this with my PKU clinic and they arranged physiological testing. The outcome was that the decline I was noticing is consistent with expectations for people with PKU. I fear I will not be able to keep up my role in my current line of work. I am the sole provider for a family of four. There is a high chance that my current project will be coming to an end this year and I do not feel that I will be capable of securing a replacement, such are the mental struggles I am facing. What then for my family?

Aside from these 'technical' issues, I also have big problems with confidence, socialising, almost paranoia. I cannot speak to a group. Given the choice, I can talk well to one person or maybe two or three at a time if I know them well. Anything more and I start to experience physical symptoms such as blushing, shakes and sweats and am unable to put my sentences together. Socially, I feel like an outcast constantly. There is no relief from the pressure of social eating. So much of our eating is now done publicly. Every single business meeting where food is provided, I have to explain at varying levels of detail, why I'm not eating, why I can't eat the food provided, what happens if I do eat it, explain why it's not like being gluten intolerant. So you just avoid it. You avoid going to restaurants. There is a huge social impact. For a large number of restaurants, chips and salad is the extent of the menu. With the sugar tax, it's now not even possible to get a soft drink many restaurants due to sugary drinks being replaced by aspartame (phenylalanine) based drinks. Of course, I could order as many spirits as I wanted and get drop down drunk with no problem but I'm unable to order a coke with sugar in, so water it is, with my chips and salad. No mixers because there's no way of knowing if the soft drinks contain aspartame. And people eat out for a treat... But that's a separate matter and just another very small example of how complicated living with PKU is.

So now, at 42, I have had four recent operations to my foot. At each one, I am asked if there is any history of neurological issues within my family history. At each one, I tell them I have PKU and they look at my blankly then proceed to tell me they need to put a screw in here, move a muscle and tendon there. No-one has the knowledge to understand the effects on the nervous system of high phenylalanine, they just try to fix the symptoms, not the cause. So today, I have difficulty walking for prolonged periods of time. This has led to me becoming pretty much sedentary. Combine inactivity with the PKU diet and that leads to weight gain. Two slices of my low-protein bread contains 360 calories. That's 360 calories for a sandwich before even adding a filling. On top of that there's three, 100+ calorie amino acid supplements to consume. So for a sandwich, with some salad and perhaps a little mayonnaise we're already at over 500 calories. Since the first operation in 2018, I have put on 20kg. Combine that with mobility issues and the future is not rosy. Until these muscular issues, caused I am told by neurological issues, I was playing football three times a week. Now I cannot walk for more than 10 minutes without pain. At every single consultation prior to an operation to fix the problems I am having, the consultant cites neurological issues as the likely cause but it is not addressed. This is the effect of 42 years of no natural protein. It is the effect of only receiving incomplete synthetic protein for your entire life. Kuvan enables PKU patients to consume more natural protein and process it. You dismiss "reduction in brain function" and the effects of phenylalanine in the blood to the nervous system as acceptable, minor ailments. These are life changing issues that will only see my dependency on the NHS increase. Kuvan could immediately reduce the amount of blood phenylalanine in my blood. My average blood level is 700 µmol per L. A "normal" person has less then 120 µmol per L. I am told my levels are good, in the top 25% for the clinic, but clearly that additional 580+ µmol per L is extremely damaging.

The appraisal suggests that the issues I am having are reversible and PKU does not cause irreversible brain damage in adults. Please let me know how to reverse this damage, caused over a number years, mostly my adult years.

430	recommendations	1 Recommendations	Also, there is not enough evidence on how sapropterin might be used to prevent harm to the unborn child in women with PKU who are pregnant or trying to conceive.	There is clear evidence that high blood phenylalanine levels caused by PKU in pregnant woman is extremely damaging to the unborn baby, This appraisal clearly states that Kuvan is effective in reducing blood phenylalanine. This statement is contradictory and makes little sense. Women with PKU live in absolute fear of getting pregnant from the minute they are of an age to be capable of giving birth. As an adult male, to be on 10g of protein a day and achieve blood levels of 700 umol per L is exceptionally difficult. To manage the pre-conception PKU diet and maintain zero levels during pregnancy is an absolutely mammoth feat that it is unreasonable to expect people to be able to manage.			No	
431	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	This diet should be continued as an adult.	The use of Sapropterin would greatly assist adults to be able to follow this extremely restrictive diet for life.			No	
432	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	However, adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25.	How can the use of Sapropterin be removed at 18 years if brain development does not stop until around age 25?			No	
433	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	In adults, high Phe concentrations can result in short-term symptoms, which are considered reversible by lowering Phe levels through diet. These include impaired executive function, reduced autonomy, impaired social maturity, difficulty forming relationships and neuropsychiatric symptoms such as depression, anxiety and inattention.	These symptoms mean that quality of life and the ability to perform high level jobs/ tasks is negatively affected. Many of these symptoms could lead to patients needing access to and support from other services in the long term, e.g. mental health services.			No	

434	committee-discussion	High blood Phe levels in pregnancy can have harmful effects on the unborn child	They noted that good control of blood Phe levels (below 200 micromoles per litre) should be maintained if possible,	The use of Sapropterin would greatly assist women to be able to reduce and maintain lower phe levels.			No	
435	committee-discussion	The only treatment option available for people with PKU is a self-managed protein-restricted diet	This includes foods that are rich in protein (for example, meat, fish, dairy products and soya), foods with less natural protein (for example, fruit, vegetables, cereals, flour or pasta) and alcoholic drinks containing protein (for example, beer and stout).	This ultra restrictive diet impacts on families and every single social event involving the person with PKU. It is not possible to eat at restaurants, parties, social occassions, holidays, etc without thorough planning and preparation. This can be embarrassing and off putting.			No	
436	committee-discussion	People with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet	Adults can have raised Phe levels because they struggle to adhere to, or have completely stopped, their diet. Clinical experts noted that just over 50% of adults with PKU are on a protein-restricted diet, while about 30% of adults have stopped their diet and the other 20% have difficulties maintaining it. Patient experts explained that being on a strict protein-restricted diet is burdensome and demanding for people with PKU and their carers for several reasons:	The use of Sapropterin in adults would enable a reduction in phe levels and therefore enable them to be better equipped to deal with the demands of the strict diet. The increase in tolerance of protein from food would also mean that there was an element of freedom introduced and this would contribute to adherence to diet.			No	

437	committee-discussion	People with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet	The time-consuming nature of food shopping and meal preparation. Also, the wide range of skills needed to understand food labels, calculate precisely, and weigh the amount of Phe in different foods that can be eaten in each meal, and prepare and cook meals regularly. This can take 2 to 3 times as long as normal and make managing the diet a dominant activity of daily life.Poor taste and disagreeable smell and texture of low-Phe foods and synthetic protein substitutes. These have to be taken in large volumes 3 to 4 times a day and can cause digestive problems.	Being able to have the choice to use regular ingredients and regular foods would make preparing foods more simple. The taste of regular foods far exceeds those of the prescription foods. To be able to eat regular foods would add an element of joy to eating that has not been there before.			No	
438	committee-discussion	There is a need for a treatment that can reduce PKU symptoms and give people with PKU and their carers peace of mind about blood Phe levels	Many adults describe the effects of high Phe levels as 'brain fog', forgetfulness, tiredness, confusion, low mood and feelings of irritability. This can affect their ability to control their diet and maintain adequate blood Phe levels	Using Sapropterin would lower phe levels and make it much easier for people to adhere to the diet.			No	
439	committee-discussion	Sapropterin is clinically appropriate and beneficial for people with PKU that responds to sapropterin	Patient experts advised that adults with PKU who have taken sapropterin report improved day-to-day functioning, particularly concentration and mood. In addition, they were able to resume other activities such as studies or work.	Adults need sapropterin for quality of life and relationships. Also for the ability to contribute to society and hold down jobs.			No	

440	committee-discussion	Sapropterin is clinically appropriate and beneficial for people with PKU that responds to sapropterin	The committee concluded that sapropterin is beneficial for those people with PKU that responds to sapropterin.	This statement is true of both adults and children. The burden of the diet is eased with the use of sapropterin in both cases.			No	
441	committee-discussion	The PKUDOS registry has evidence for long-term efficacy of sapropterin plus protein-restricted diet for the whole PKU population and is generalisable to the NHS	The committee concluded that only the PKUDOS registry provides evidence for long-term efficacy of sapropterin plus protein-restricted diet compared with diet alone in the whole PKU population.	This shows that sapropterin is effective in adults as well as children and should therefore be used by both.			No	
442	committee-discussion	The sapropterin dose used in clinical practice in the UK would be lower than used in the PKUDOS registry and in line with European practice	The committee concluded that the sapropterin dose used in clinical practice in the UK would be less than that used in the PKUDOS registry and more in line with European practice.	The dose should be dependant on individual needs. Medics need to be given flexibility when prescribing.			No	

443	committee-discussion	The additional utility gains modelled by the company for all women of childbearing age are not supported by evidence	The patient and clinical experts further added that treatment for pregnant women with PKU could be improved, because they felt the current NHS policy meant pregnant women were having treatment too late (see section 3.2). The committee considered that the effects of uncontrolled Phe levels on the unborn child may be substantial by the time women become aware they are pregnant and then show uncontrolled Phe levels with a protein-restricted diet. It considered that the maximum benefit of sapropterin during pregnancy would be obtained by it being available from conception. T	This supports the idea that adults need access to sapropterin. A woman can experience an unplanned pregnancy and if she were to already be taking sapropterin then the unborn child would be protected.			No	
444	committee-discussion	Higher doses than 10 mg/kg for children and 12.5 mg/kg for adults would have a significant effect on the cost effectiveness of sapropterin	The committee concluded that escalation above the dose of 10 mg/kg for children and 12.5 mg/kg for adults would have a significant effect on the cost effectiveness of the treatment.	Patients should be prescribed the amount which is most effective as an individual. Medics should be allowed to use their judgment.			No	
445	committee-discussion	A 10 mg/kg dose in children and 12.5 mg/kg in adults, and a 71.2% reduction in protein-restricted diet is acceptable	adolescents and unborn babies from poorly controlled Phe levels.	Adolescent and adult women should be given access to sapropterin to help control phe levels.			No	
446	committee-discussion	Sapropterin has not been shown to be cost effective in adults with PKU	Therefore, costs of sapropterin are much higher in adults than children	Adults with PKU should not be penalised due to company greed.			No	

447	committee-discussion	Sapropterin has not been shown to be cost effective in adults with PKU	he additional consideration of the risk of irreversible brain damage did not apply to the adult population.	Your policy states previously that brain development continues to the age of 25 years.			No	
448	committee-discussion	Sapropterin is not recommended in adults with PKU for treating HPA that has been shown to respond to sapropterin	and there is no risk of long-term brain damage in adults.	Although there is no risk of brain damage there is an affect on the brain which leads to other symptoms. These symptoms prevent PKU patients from living a normal life and contributing to society as well as they could.			No	
449					Has all of the relevant evidence been taken into account?	The Scottish IMD Service welcome the NICE recommendation to treat children with phenylketonuria (PKU) who are responsive to Sapropterin as they will benefit from its use and reduce the burden of following a complicated and restricted protein diet. However, we are concerned with the recommendation to discontinue Sapropterin at 18 years of age when elevated phenylalanine will be detrimental to cognitive function at a time when maintaining blood phenylalanine control continues to be important. Many young people go into further education, start employment and move out of home for the first time. There is evidence that the brain does not fully mature until 25 years of age. In particular, “executive functions” such as planning, working memory, and impulse control, are among the last areas of the brain to mature and may not be fully developed until halfway through the third decade of life (Sowell R, 1999). Chronic elevated blood phenylalanine is known to adversely affect executive function in individuals with PKU. Individuals who have been on Saproterin throughout childhood will not have adapted to following a highly restrictive diet or have the necessary skills to independently manage the diet introduced later in life. Introducing this restrictive diet at this time would be disruptive and add additional stress and anxiety at this key life stage. In order to protect brain development and ensure optimum cognitive function throughout the educational years and through the major life events of early adulthood, we would like to see the recommendation that Saproterin treatment can continue until at least 25 years of age. Uncontrolled blood phenylalanine is a concern during pregnancy. Women are advised to tightly control their blood phenylalanine levels prior to conception and maintain control throughout their pregnancy to avoid the teratogenic effect of elevated phenylalanine. Women are encouraged to continue dietary management after pregnancy in order to better cope with the demands of being a new mother. Many women are highly motivated to adhere to dietary recommendations for pregnancy but struggle to maintain control if they develop pregnancy related nausea and vomiting. If women have not adhered to a low protein diet before, they could struggle to follow the demands of a very low protein diet for a safe pregnancy. Health consequences of maternal PKU syndrome include intellectual disability, autistic spectrum disorders, congenital heart defects and attention hyperactivity disorder. Consequently, the benefits of newborn screening for the early identification of PKU and some of the	Yes	Scottish Inherited Metabolic Disorders Dietetic Service

						benefits of using Sapropterin up until 18 years of age are then lost for the child born with the health consequences of uncontrolled phenylalanine levels in the mother. At present, Sapropterin can be provided in pregnancy after standard measures have failed but often this is weeks into the pregnancy at which stage damage to the fetus will have occurred. A high level of care should continue after birth to prevent the symptoms of high levels at an already difficult time with a new baby. We would like to see the recommendation that women who plan a pregnancy are assessed for their responsiveness to Sapropterin and are treated with it during preconception, throughout pregnancy and for a period of time after birth.		
450					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	The cost effectiveness of maternal PKU syndrome has not been reported. From personal experience, children born to mothers who had poor metabolic control throughout their pregnancy and that have severe physical and learning disabilities have required regular appointments with a community paediatrician, occupational therapist, paediatric dietitian and physiotherapist and must attend nurseries and schools specially equipped to support children with special needs. Parents have required additional financial support and provision of suitable housing. We would like to see the recommendation that all women of child bearing age be assessed for Sapropterin responsiveness and that those who are responsive are offered the use of Sapropterin as a first line option when they are actively planning a pregnancy and can continue it throughout their pregnancy.	Yes	Scottish Inherited Metabolic Disorders Dietetic Service
451					Are the recommendations sound and a suitable basis for guidance to the NHS?	We would like to see the recommendation that all women of child bearing age be assessed for Sapropterin responsiveness and that those who are responsive are offered the use of Sapropterin as a first line option when they are actively planning a pregnancy and can continue it throughout their pregnancy.	Yes	Scottish Inherited Metabolic Disorders Dietetic Service

452					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	We feel that withdrawing treatment based on age is discriminatory. The NICE proposal contradicts and undermines the current recommendation that dietary treatment should be lifelong (Van Spronsen et al, 2017).	Yes	Scottish Inherited Metabolic Disorders Dietetic Service
453					Has all of the relevant evidence been taken into account?	I work as a clinical lead Dietitian in the All Wales Inherited Metabolic Disease adult service. The population I reference here includes 63 adult patients with PKU under ongoing follow up by our All Wales Inherited Metabolic Disease Specialist centre. It does not include those patients lost to follow up or the North Wales cohort. No, it has not. There is higher incidence of medical and psychological issues in adults with PKU compared to non-PKU controls, such as anxiety, depression and osteoporosis (Brumm et al. 2010; Ford et al. 2018; Green et al. 2019). 36 % of our adult PKU population live with a known mental health condition with the vast majority of these requiring some form of anti-depressant / anti-anxiety medication. There is evidence that brain development continues up until ~25 years of age and yet the proposal to stop this medication at 18 overlooks this. Evidence of the risk of maternal PKU syndrome and the catastrophic potential effects on babies born to uncontrolled PKU mothers has been grossly overlooked. Only 37% of our adult PKU population achieve target phenylalanine (phe) control. This leaves the remaining 61% outside the target range and often living with the known side effects of elevated phe control such as difficulties with executive functioning, mood, concentration. Brumm, V. et al. 2010. Psychiatric symptoms and disorders in phenylketonuria. Molecular Genetics and Metabolism Reports 99, pp. S59-S63. Ford, S. et al. 2018. Living with phenylketonuria: lessons from the PKU community. Molecular Genetics and Metabolism Reports 17, pp. 57-63. Green, B. et al. 2019. Nutritional and metabolic characteristics of UK adult pheylketonuria patients with varying dietary adherence. Nutrients 11, pp. 3-13.	Yes	Dietetic Departmen t: All Wales Adult Inherited Metabolic Disease Service

454					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	Not all of the potential cost savings for offering this drug to adults have been considered. As discussed 36% of our patients are living with a known mental health condition, often requiring anti-depressant / anxiety medication. The potential cost savings around this are vast. We have seen cases with patients returning to diet, improving their phe control, coming off antidepressants and being able to return to work. If you were to extrapolate this across the UK PKU population the summative affect would be significant. The potential cost savings to the health service and to society of people with PKU coming off state benefits and getting into employment, the reduced costs of antidepressant / anxiety medication, reduction in days of work lost. Furthermore, a number of our patients require the support of counselling or psychology services. Again, these costs would be markedly reduced should Sapropterin be available as a treatment option for them. There are also cost savings around prevention of nutritional deficiency from over restricted or combination diets which often result in the need for interventions such as IM B12 injections, calcium and vitamin D supplementation for osteoporosis etc.	Yes	Dietetic Department: All Wales Adult Inherited Metabolic Disease Service
455					Are the recommendations sound and a suitable basis for guidance to the NHS?	No, I do not believe that they are. They are unethical and discriminate on the basis of age, gender and further disadvantage those living with a disadvantage – see below.	Yes	Dietetic Department: All Wales Adult Inherited Metabolic Disease Service

						Discrimination on the grounds of age: Established new born screening, successful paediatric management and the consensus recommendation of 'diet for life' have given exponential rise to an adult PKU population (Dermirkol et al. 2011; Van Spronsen et al. 2017). These service users, historically managed via paediatric services, now require care via specialist adult, metabolic centres (Demirkol et al. 2011). This evolution has introduced the phenomena of 'transition' for these young adults specialist adult centres. The evidence and guidelines now recommend that people with PKU should remain on diet for life (Van Spronsen et al 2017). Therefore, how can the recommendations propose that Sapropterin, a treatment for this condition which requires lifelong treatment, be withdrawn at age 18? This discriminates on the ground of age. Moving from teenage years to adulthood is a testing time, particularly so for those with chronic conditions adjusting to changes in their healthcare provision (Campbell et al. 2016). Brumm et al. (2010) describes how young adults with PKU display less autonomy than non-affected peers, alluding to the additional challenge transition presents for them. There is an association between transition and worsening health in this age group (Campbell et al. 2016). In accordance with the literature, our clinical experience concurs that a number of adolescent PKU patients do not attend their first adult clinic appointment post transition and display less dietary adherence and sub-optimal phe control (Cazzorla et al. 2018; Green et al. 2019; Kramer et al. 2020). At age 18 a number of young people are going through dramatic life changes and moving from a period of dependence to independence. They may be moving away from home to go to college or university and may start to manage their PKU more independently for the first time. We see from the number that can disengage with healthcare services through the later teenage years that this is a hugely challenging time. Discontinuing a drug at this time point could have catastrophic effects, with patients potentially having to learn strict dietary management of PKU whilst coping with all their other life challenges. The reality is that this is unlikely to be successful. Patients may find themselves in a 'grey' area: without Sapropterin but neither fully 'on' nor 'off PKU diet. Nutritional deficiencies will arise and females will be at risk from suboptimal phe control and in turn the catastrophic risk of uncontrolled, unplanned pregnancy outcomes. Comparing PKU with other chronic, lifelong conditions such as Diabetes type 1, you would not imagine starting dietary management at 18 for the first time. Discrimination on the grounds of gender: 39 patients (62%) of our active adult PKU caseload are female. We manage approximately 2 PKU pregnancies each year. At present we have 2 pregnant patients and another 3 who are striving to achieve optimal phe control before they start trying to conceive. This equates to 8% of our adult population struggling to maintain phe in the 120-300umol / l target range at any one time. The pressure that this strict dietary control places on women at an already stressful time of their lives is apparent. Trying to conceive for many women is not straight forward. Having to share this intent so publicly with their metabolic teams, friends and family and place such scrutiny on their diet often heightens anxiety and negativity at what should be an exciting time (Ford et al 2018). Discrimination on the grounds of learning disability: We have 63 adult patients with PKU under active follow up at out		
456					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?		Yes	Dietetic Department: All Wales Adult Inherited Metabolic Disease Service

						All Wales IMD specialist centre and receive 2-5 new referrals / year, made up of transitions from paediatric services and new referrals for patients wishing to return to diet or late treated individuals looking for improved QOL. 8 % of are adult patients are late treated PKU, diagnosed later in life after the introduction of new born screening. All of these patients live in supported care facilities and have profound learning disabilities. Most of these patients will never have tried a low protein diet or the low protein substitutes vital to complete the dietary management. Later in life tastes and habits are well formed and particularly in individuals where there may already be behavioural difficulties, introducing or changing an established diet and lifestyle can be extremely challenging. Evidence and anecdotal experience demonstrate the benefit of phenylalanine control via a low protein diet etc on parameters such as behaviour, social skills, communication and overall an improved quality of life (Lee et al 2009). In omitting this group of people they are being denied the opportunity to enhance their quality of life and are therefore victims of discrimination. Were these people afforded Sapropterin as a treatment option they could see profound improvements in their QOL, which in turn could lead to reduced care costs around medications, support workers etc. 22% of our adult population are recognised as having a learning disability; already living at a disadvantage. Discrimination on the grounds of socio-economic group: Lower socio-economic groups tend to do less well with dietary management in chronic conditions. 5% of our patients are from traveller communities and already living with a recognised life disadvantage in this respect. Brumm, V. et al. 2010. Psychiatric symptoms and disorders in phenylketonuria. Molecular Genetics and Metabolism Reports 99, pp. S59-S63. Campbell, F. et al. 2016. Transition of care for adolescents from paediatric services to adult health services. Cochrane Database of Systematic Reviews. Available at: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009794.pub2/full [Accessed 22nd February 2020]. Cazzorla, C. et al. 2018. Living with pheylketonuria in adulthood: The PKU ATTITUDE study. Molecular Genetics and Metabolism Reports 16, pp. 39-45. Demirkol, M. 2011. Follow up of phenylketonuria patients. Molecular Genetics and Metabolism Reports 104, pp. S31-S39. Ford, S. et al. 2018. Living with phenylketonuria: lessons from the PKU community. Molecular Genetics and Metabolism Reports 17, pp. 57-63. Ford, S. et al. 2018. Reproductive experience of women living with phenylketonuria in the UK. Molecular Genetics and Metabolism Reports 17, pp. 64-68. Kramer, J. 2020. Sustaining benefits of nutritional therapy in young adults with pheylketonuria - A 2 year prospective study. Molecular Genetics and Metabolism Reports 22, pp. 1-6. Lee, P.J et al (2009) Adults with late diagnosed PKU and severe challenging behaviour: a randomised placebo-controlled trial of		

						phenylalanine restricted diet. Journal of Neurology and Neurosurg Psychiatry. 80, pp 631-663. Margolis, R. et al. 2017. Transition from pediatric to adult care by young adults with chronic granulomatous disease: The patient's viewpoint. Journal of Adolescent Health 61, pp. 716-721. Van Staa, A.L. et al. 2011. Crossing the transition chasm: experiences and recommendations for improving transitional care of young adults, parents and providers. Child: Care, Health and Development 37(6), pp. 821-832. Van Spronsen, F. J. et al. 2017. Key European guidelines for the diagnosis and management of patients with phenylketonuria. The Lancet Diabetes & Endocrinology 5(9), pp. 743-756.		
457				I urge you to consider over 18s the receive kuvan, do our brains not matter?!.. Have you considered treating pregnant women with PKU... Imagine your already severely strict diet halved at a time you are growing a human?! Also I ask the question re: dosage is there a reason the dose has been capped? The BNF clearly states doses of 20mg/kg may be required? Additionally if you ignore my previous comments, explain have the stopping Kuvan at 18 will work? PKUers without the experience of following their low protein diet have the treatment removed just as they are about to go to university or out into the world?!			No	
458				Extremely happy to see the drug will be issued, but having seen my friend organise every single thing that crosses her son's lips- would it not be better if doses were personalised, so those with PKU won't have PKU still determining their diet? Also, what happens when a child hits 18? I can't see how ethically the drug can be removed from them?			No	
459				It's amazing that after a long campaign you have finally decided to let Kuvan be available for children who suffer from PKU. It is a pity that Kuvan will only be available till children turn 18. Most children have supportive, caring parents who help them manage their PKU and at 18 when they are starting their adult life and becoming independent their support of Kuvan is taken away. As you are aware Kuvan doesn't for all children/ people so why can't all the individuals that it works on have their full amount they need for their whole lives.			Yes	School
460					Has all of the relevant evidence been taken into account?	I feel that the committee could have sought further information from those who have had access to Kuvan as part of a trial and then had this removed, showing the significant negative impact this has had on them.	No	

461					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	I feel there is a lack of appreciation of the impact of raised phenylalanine levels on those over 18.	No	
462					Are the recommendations sound and a suitable basis for guidance to the NHS?	I believe that Kuvan should be offered to those over 18.	No	
463					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	I believe this decision particularly impacts women due to the need to maintain very low phenylalanine levels in pregnancy, which will be particularly difficult without access to Kuvan.	No	
464				I welcome the decision of NICE to offer Kuvan to under 18s. However I strongly believe Kuvan should also be offered to those over 18. It seems extremely cruel to remove a medication which will have a significant impact on an individual's wellbeing and lifestyle just as they are entering adulthood. To change the diet to one which will be significantly more restrictive in terms of protein allowance will be very difficult and a lot of people will not be able to sustain this. This will lead to the negative impacts on cognitive functioning and fetal wellbeing discussed late in this document. Those with PKU want to live full and active lives contributing fully to society, and removing access to Kuvan at 18 will significantly impact on their ability to do so.			No	
465				Although it's good to see that this treatment has been given some kind of go ahead, it seems that the usage is quite restrictive. The dosage is vapped at half of what would be an efficient treatment for many, and the fact it's only available until age 18 seems to be such an oversight given that turning 18 doesn't stop the symptoms of PKU. Suddenly having to adapt to a very restrictive diet as a teenager would be quite difficult and dangerous if you've recently embarked upon independent living for the first time. Its good that this treatment may be available for the first time, but the circumstances surrounding its usage need to be broadened to include the full recommended dose in other countries, and people above the age of 18 for whom its making a marked difference to the management of their condition.			No	
466				My daughters 8 years old, she has classical pku and manages around 7g of protein per day. If she was responsive to KUVAN she could have a normal diet but how can we expect children to live a normal life with a normal diet then take it all away once they turn 18?			No	
467				It is wonderful news that Kuvan has been recommended for use for PKU patients. However it will be a bittersweet success for those parents and patients, such as my close friend who has been battling for Kuvan for her son for all of his 6 years. The recommendation to only supply this to under 16s is surely discriminatory, at a time in a young adults life when they are looking to explore the world and live independently, to prevent treatment which will no doubt allow them to socialise with their peers more easily. Stan comes to my sons parties and we are only to happy to cater for his needs, often at additional cost and only because we have advice from his mom. As an 18 year old, it would put him in an embarrassing situation to have to demand a very particular diet. Also the decision to limit dosage where every study and advise on Kuvan recommends flexibility to suit the patients individual needs and response to the drug surely makes the decision to administer it, null and void. I would liken it to allowing Stan to eat at a buffet but tying his hands behind his back. It is surely most cost effective to administer a dosage suitable for the patient with a greater degree of success than to administer a standard dose which may only be effective 50% of the time.			No	
468					Has all of the relevant evidence been taken into account?	- Dose of 10mg/kg recommended however clinical trial our team were involved in, the patient responded to 20mg/kg.	No	

469					Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	- The evidence only looks at cost of drug minus the cost of the diet. This does not take into account the cost of counselling/ psychological support. The patient's loss of work time needs to be considered. - If the medication is stopped at 18 years of age the individual will need education on dietary management for their condition.	No	
470					Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	Stopping the drug at 18 years of age is unethical. There are significant life changes at 18 years of age such as sitting exams which affect future employment, going to university, doing apprenticeships, starting work, moving out of the family home, becoming more independent. For a young person to have to change their diet at 18 years of age because a drug has been stopped would put significant stress on the individual. The individual would need to adapt their diet and depending on how long they had been on the medication for would depend on how easy they would know how to do that. The patient would need to have education on this. The individual would struggle psychologically with this. 18 year olds already have a great deal of stress placed on them without this significant burden. If phenylalanine levels are high at this time this would affect learning, exams, mental health (anxiety). (van Wegberg, A.M.J. et al. 2017). MacDonald, A. et al. (2010) acknowledges that the best measure of compliance is the number of phenylalanine levels within the target range. It has been found that teenagers and adults have higher quantities of phenylalanine levels, above the desired range, indicating a decrease in compliance with age (MacDonald, A. et al. 2010). At diagnosis and during childhood the treatment of PKU is managed by the main care givers. Carpenter et al. (2018) explored the parental experience of having a child with PKU and reported that one of the common sub themes described by parents was their fear of the consequences of non-compliance in the long term. This could explain why compliance during childhood is often not an issue but becomes an issue as the person with PKU ages and has more control over their chronic condition. - Starting the medication is a very difficult decision for the families of 12+ year olds to make. Do you start a medication for your child which may improve their quality of life/ diet to then understand that they will have it taken away at 18 years of age. This puts a psychological burden on families. - There is evidence that brain development continues until 25 years of age so why is the medication being stopped at 18 years of age. These 7 years of brain development are still crucial. We also know that adults with PKU who have high phenylalanine levels struggle with low mood, depression and anxiety. Mental health is not being taken seriously. - There is no evidence that the medication should be stopped. Treatment for life. - Unfair on women with PKU who are pregnant. It is important that women with PKU have good control of their phenylalanine levels for the unborn child's development. This group of patients are not being given the best chance.	No	
471				As parents to a newly diagnosed 11 week old little girl with PKU, the prospect of her expanding her diet with Kuvan comes with great relief. But how can she go through life for 18 years and then be expected to alter he entire way of living? It is not possible to teach a child a way of life that they do not yet live. This is a condition she has for life not for 18 years.			No	

472	committee-discussion	Recommending sapropterin for certain groups of adults cannot be justified given the cost-effectiveness estimates	The committee considered that a positive recommendation for children but not adults was appropriate based on differing disease risk and cost-effectiveness estimates.	Adults suffer from the above concerns			No	
473	committee-discussion	PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain and reversible neurological changes in adults	Clinical experts explained that brain development peaks at around age 12. After this high Phe levels are unlikely to affect IQ. However, adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25	This information seems contradictory, if brain development continues until 25, why will the medication not be available after the age of 18?			No	
474	committee-discussion	High blood Phe levels in pregnancy can have harmful effects on the unborn child	The experts explained that Phe levels should be kept low throughout the whole pregnancy. Dietary measures should ideally be started before conception to avoid congenital effects, but at least at the earliest possible opportunity to avoid harmful effects on the unborn child.	Access should e available prior to conception so that blood levels were controlled therefore reducing risk, stress and pressure, as well as danger to unborn child			No	
475	committee-discussion	High blood Phe levels in pregnancy can have harmful effects on the unborn child	But they are not ideal, and the current NHS policy is not optimal. The committee concluded that high blood Phe levels in pregnancy can have harmful effects on the unborn child	Again, surely this is why it is so important to ensure access is available. Otherwise we continue down an irreversible cycle with each new generation			No	

476	committee-discussion	People with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet	The committee concluded that people with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet.	There is also impact on other areas such as struggling to eat out and integrate with people following an unrestricted diet, problems with school meals, constant explanation of what is required, a constant worry that people won't get the diet right. It's non stop stress and pressure			No	
477	committee-discussion	There is a need for a treatment that can reduce PKU symptoms and give people with PKU and their carers peace of mind about blood Phe levels	Some adults are unable to engage in full-time work because it creates a vicious cycle of less time to control diet and higher Phe levels, leading to reduced ability to focus and organise the diet	The impact of removing the drug at 18, would be that PKU sufferers would not be able to hold down a more demanding job and contribute to society. This would have an effect on themselves, family, friends and the economy and present discriminatory/equality concern			No	
478	committee-discussion	There is a need for a treatment that can reduce PKU symptoms and give people with PKU and their carers peace of mind about blood Phe levels	The committee concluded that there is a need for a treatment that can reduce PKU symptoms and give people with PKU and their carers peace of mind about blood Phe levels.	This should not be removed at the age of 18, it is unethical and would result in greater issues in later life when development of social skills, further education, employment, starting a family shape an adults life/ Taking this away would threaten to reduce the opportunities and wellbeing to PKU adults			No	
479	committee-discussion	Sapropterin is clinically appropriate and beneficial for people with PKU that responds to sapropterin	Patient experts advised that adults with PKU who have taken sapropterin report improved day-to-day functioning, particularly concentration and mood. In addition, they were able to resume other activities such as studies or work. Parents of children with PKU report similar benefits in the mood, energy, concentration and behaviour of their children	This in itself is reason that the availability of the drug should continue for the life of a PKU sufferer. Removing the drug at such a critical stage in life is unethical			No	

480	committee-discussion	The trial evidence shows sapropterin plus protein-restricted diet is clinically effective compared with protein-restricted diet	Results from the RCTs show that patients having treatment with sapropterin plus protein-restricted diet significantly reduce blood Phe concentration levels and maintain target levels compared with patients having diet only.	How can the evidence of the trials be ignored? The outcome of the trials have shown the benefit but it appears that evidence led research isn't followed in this example			No	
481	committee-discussion	The sapropterin dose used in clinical practice in the UK would be lower than used in the PKUDOS registry and in line with European practice	Clinical experts further explained that increasing sapropterin dose does not improve efficacy because response to sapropterin primarily depends on the level of PAH activity and mutations, not the dose.	The dose should be based on individuals needs rather than a "suits all" approach			No	
482	committee-discussion	The estimate of 71.2% reduction in protein-restricted diet is not evidence-based	forthcoming systematic review.	How can it be referenced/cited - if it is forthcoming and not complete?			No	
483	committee-discussion	The estimate of 71.2% reduction in protein-restricted diet is not evidence-based	The committee concluded that it seemed likely that patients would reduce their protein-restricted diet, but it could not be certain that the reduction would be as high as 71.2%	It seems that evidence needs to be clearly followed rather than guess work. Contradictory to follow it some times and ignore it at others			No	
484	committee-discussion	Long-term brain damage in children is an important aspect of PKU, but there is little evidence to estimate its effect on quality of life	However, information is not routinely collected on long-term brain damage because of PKU or the number of children referred to early help services and social services, and the costs involved	The costs involved with long term treatment of issues caused by the PKU diet would far outweigh the cost of the drug			No	

485	committee-discussion	The utility values from the time trade-off study are highly uncertain, but are the only available evidence	Quality of life was not assessed in sapropterin studies because of difficulties in measuring it in people with PKU	Case studies?			No	
486	committee-discussion	The methods used to calculate health state utility values are inappropriate and make the utility values highly uncertain	The clinical experts pointed out that there are patients with severe PKU symptoms and an IQ below 50, but with good care provision their quality of life would not be expected to be so poor as to be close to death. However, 1 patient expert confirmed that they are aware of a patient with severe symptoms and a learning disability who has communicated that they wish to die on several occasions	This should be reason enough for a decision to continue the drug past 18			No	
487	committee-discussion	The costs of protein-restricted diet estimated by the company are reasonable, but the cost savings with sapropterin are uncertain	The ERG produced 2 scenarios with 0% and 71.2% reductions. The committee concluded that the cost savings related to a reduction in protein-restricted diet are uncertain	But the savings in every other area would be significant and the long term impact of removing the drug at 18 would have socio economical, financial, mental health issues			No	
488	committee-discussion	Sapropterin is not recommended in adults with PKU for treating HPA that has been shown to respond to sapropterin	Therefore, it concluded that sapropterin is not recommended in adults with PKU for treating HPA that has been shown to respond to sapropterin.	The dose should be based on an individual basis determined by specific needs of each sufferer			No	

Sapropterin for treating phenylketonuria [ID1475]

Comments on the ACD received from the public

Name	
Comments on the ACD:	
My grandson was diagnosed at birth with PKU. This came as a huge shock and filled us with fear as to how we were going to manage the restricted and complicated dietary therapy that he would be on for life...my daughter found it very hard as it was her first baby.. and at that time there was no help available through support groups on social media and there were very few other mothers out there that she could talk to... she felt very alone and vulnerable. When my grandson was about 6 months old, I made the decision to give up my career with a large insurance firm where I had been employed for 21 years, and help my daughter with her young baby as she was struggling to cope. This meant, I gave up my salary, my pension and other benefits of being at work because this condition was so hard to manage on a daily basis. I accompanied my daughter and grandson to his regular PKU Clinics at Great Ormond Street and learnt how to cook with the PKU prescription products so that I could cook meals for him. It was stressful looking after him as I was responsible for keeping him safe whilst his mum was at work, and all that that entailed. Since the age of about 6 or 7 years, he was told he would be eligible for this new life-changing drug, Kuvan! This of course was wonderful news for all the family! (since PKU is a condition which affects ALL the family and not just the PKU sufferer themselves, and this is true whatever age the PKU sufferer is). We have closely followed the 12 year old battle to get an this alternative drug treatment for PKU and lived the ups and downs with him whilst it has repeatedly been refused. Finally, NICE has taken the decision to commission Kuvan but my grandson, and many others like him, is now in his 20's and has been given the bitter blow that, under your draft Guidance, he would not eligible for this drug because of his age. Starting children on a medical therapy of Kuvan and then taking it off them at 18 is nothing more than cruel and senseless. From experience with my grandson, adolescence for some one with PKU presents so many difficulties. For my grandson, he began to experience mental health issues and in a vicious circle, began to reject the diet and withdraw himself socially. He became very depressed and struggled through school. This was a worrying period for my daughter and the whole family as, as he turned 18, we no longer had control of his compliance to the dietary therapy and he began to spiral into a vicious circle of depression and severe anxiety. My daughter resorted to home education and private tutors and with extreme perseverance, he got a university place. However, he struggled to cope with his PKU - he was leaving home for the first time to attend university several hours away, struggling to get on top of his mental health, managing his prescription foods, organising deliveries from the chemist, coordinating his own medical appointments, cooking the foods, storing all the foods and medication he needed, learning to study independently, manage his lectures and timetabling, housework etc - all by himself for the first time, which was extremely daunting for him! Although, my daughter supported, encouraged and prompted my grandson to the best of her ability with managing his PKU, he found it very difficult and failed his first year exams. He then had to take time out from uni and come back home where my daughter helped him get back on top of his health. He was	

given a special dispensation and was allowed to continue to do his second year studies, however, despite all the family's best efforts, the PKU got the better of him again and once again, he had to drop out of uni. Throughout this period, he has been seen by adult mental health care services and received therapy for depression, social withdrawal and anxiety. For my grandson, it was clear that the only way he would be able to finish his degree would be to transfer to a local university where he could live at home whilst he studied, be supported by his family to manage his condition and attend therapy for his mental health. I'm sure that there are many other young PKU adults out there like my grandson who, are starting out in life (doing their A levels, going to University or embarking on a new career or apprenticeship.. quite possibly even in the medical field or teaching etc) and for whom it would be disastrous to interrupt their medical treatment at this stage of their lives. We
must remember that these young people are our future and their education is valuable to society! Their brains do not stop developing at 18! In fact, we've read that the human go even , a family friend of ours suffered a severe brain injury at 40 and MRI scans showed he lost half his brain -- yet , with rehab and hard work, he has redeveloped new areas of brain growth and adapted other parts of his brain so that now he can walk and talk, - something which the neurosurgeons said would be physically impossible for him to do! This personal story shows that there is so much we humans don't yet know about the human brain and to deprive anyone with PKU over the age 18 a chance to an alternative, new therapy other than dietary therapy, is a sign of ignorance and lack of foresight. I refer to years back, when you used to take PKU children off the dietary therapy as young as age 8 - you now know that this was the wrong thing to do and those poor children are now adults with learning difficulties, mental health issues and various other disabilities which they would not have had you had the foresight not to take them off diet before their brains had finished growing. By stopping a successfully Kuvan-treated 18 year old, you are making the same mistake again and potentially ruining the lives and quality of lives of all those young people and all their families who are equally affected. When you have a child with PKU, it is for lifeand the whole family has PKU in their lives for life! We strongly feel that PKU patients, no matter what age they are, deserve to be given the best chance in life and to be given the opportunity of having a drug which will help them manage and cope with their lives on a daily basis. Your draft Guidance shows a horrendous lack of misunderstanding about PKU - the reality of living with this condition and how it actually affects sufferers and their families. There could be swathes of academic papers out there with graphs and charts, but we, the PKU families, see the reality behind living with this condition and let me tell you, it is LIFELONG!

I find it hard to comprehend that, given there are only 2250 PKU sufferers out there (of which only 675 / 30% might be a "responder" to Kuvan), NICE is not giving each and everyone of them a chance to see if this new drug works for them. Furthermore, with the on-going research taking place in the medical field and the possibity in the future of gene therapy, we may in time see the number of people with PKU decrease. So why not look after the 2250 patients you have with the condition NOW? Out of the millions that the NHS spends on people with various conditions, it is morally and ethically wrong for you to cost cut for people with PKU just because it is a rare disease.

May I quote from the Ministerial Foreward of the Department of Health and Social Care's 5 Year Strategy on Rare Diseases in which our Governments says : "The UK Strategy aims to ensure no one gets left behind just because they have a rare disease. We want to put the patients' needs first". We expect this Strategy to apply to PKU patients of all ages, not just other rare diseases! It's not my grandson's

fault that he was born with this rare disease! It's not his fault he was born before research was successful in producing this drug that could change his life! It's not his fault that he struggles to adhere to the dietary therapy that he hates so much and is therefore currently living with the crippling effects of under-treated PKU!

Me and his grandfather see first hand what this decision has done to him, how devastated he is by it and how he feels abandoned by our National Health Service. He has told me that Kuvan would be available to him in more than 50 other countries world-wide so he is now thinking about leaving the UK just so he can have access to new and modern treatments for his condition. Again, your decision, as it stands, would affect the whole family, as we would see our grandson moving abroad just because you have refused to make new treatments available to him. We urge you to amend your draft Guidance to make KUVAN available to PKU patients of all ages.

Name	

Comments on the ACD:

I am writing to express my deep concerns about the draft Guidance you have issued for Sapropterin/Kuvan for PKU. My sister's eldest son, my nephew, was diagnosed at birth with PKU. He is now 22years old. Since he was born, our whole family have become familiar with and affected by PKU. I have two daughters who are similar in age to my nephews and our family gatherings and children's playdates, which always revolve around food, have always had to work around my nephew's diet. When we babysat my nephew, we were given a note pad of instructions and told to record everything he ate and drank, a set of weighing scales to measure out his exchanges and boxfuls of the various PKU prescription foods and amino acid supplements he had to take. It was always complicated and time consuming. I know his starting school was a very scary time for his parents and they lived in constant fear of mistakes in his diet and causing him irreversible brain damage. I saw how obsessed my sister became with food, how muchtime, emotional strain and constant hard work it took to keep my nephew safe. This iswhy I applaud your decision to approve the use of Kuvan in children. I am 100% sure this will be life-changing for many families living with PKU.

However, your decision to stop giving Kuvan to people with PKU at age 18 is a dreadful lmistake and one I beg you to rethink. In the case of my nephew, I have seen first hand what the effects of PKU has on adolescents and their family. My nephew began to suffer mental health problems in his mid teens and as he approached his late teens, he began to reject his PKU diet. My sister, and indeed the whole family, have been devastated by his non-compliance to the diet and the loss of parental control over his well-being. You can lead a horse to water but you can't make it drink! We have watched as his mental health (depression, sleep disorders, anxiety, social withdrawal) has spiraled out of control and into a vicious circle of the effects of untreated PKU and mental health issues.

My nephew's secondary education suffered greatly as a result; he is a bright lad but has been unable to complete university. It is a hard time for any teenager off to university and fending for themselves the first time - a steep learning curve, ...but what a huge ask it is for an 18 year old with PKU! On top of everything else, this will be the first time that they will have to manage their condition all by themselves without the watchful eyes of their parents;- registering with a brand new GP who

may be completely unfamiliar with PKU and relunctant to order presciption foods without giving them the 3rd degree, stock management and storage of their PKU foods and supplements, cooking PKU foods (for example, making bread from PKU flour is an art form and takes years to perfect), making and managing their medical appointments, arranging collections and deliveries from the chemist, keep physically fit on a drab, time-consuming, unpalatable low protein diet! A lot of this takes confidence - my sister has been used to fighting for her son's rights since he was born, but he is shy and doesn't like to cause a fuss or draw attention to himself. He also was unable to deal with the social aspect of university to the point where he completely socially withdrew. Many times, it got too much to bear and he had to come home under traumatic circumstances. In fact, due to his PKU, he had to quit his university studies and he is far from being the only PKU sufferer who has gone through similar in their late teens.
Since he was a little boy and learnt about Kuvan at his Great Ormond Street clinic appointments, he was looking forward to the day when he could try the new life-changing drug, Kuvan! As a family, we have signed every petition and follow the NSPKU's fight to get it made available in the UK for the past 12 years. So , to say that adults with PKU and their families are "**disappointed**" by your draft Guidance to only make Kuvan available to sufferers under the age of 18 is possibly themost condescending understatement I have ever heard. Having seen how PKU affects my nephew and my family and how difficult and sometime impossible it is to adhere to dietary therapy as a young adult, I believe the decision to stop treatment at 18 is horrifically WRONG and, as a family, we would hate to see other families of teenagers go through what we have gone through.

The risks of cognitive impairment, depression, anxiety, white matter changes in the brain, low bone density and neurological impairments remain a significant issue for adult PKU sufferers as does the additional complications of non-compliance to diet for whatever reason (and there are multiple reasons for this, including disability, mental blocks, therapy fatigue, mental health, intolerance to the products etc). These horrendous effects follow PKU sufferers through to their life and can affect their ability to hold down jobs, their relationships , their self-confidence and sense of self-worth, their ability to socialise normally....
And it is extremely difficult to get back onto dietary therapy once you have been on are laxed diet. The superhuman strength is takes to go back onto dietary therapy is and for many, it simply won't be possible. PKU sufferers over the age of 18 should not be made to feel a failure if they cannot adhere to the dietary therapy.....and more importantly, they should not be left with untreated or undertreated PKU with no alternative treatment option, when such an alternative option exists, just because of their age. This decision can only be described as cruel and inhuman and is likely to induce further mental health issues in PKU adults who are already vulnerable. Whilst some of the effects of brain damage on PKU adults may be reversible by resuming dietary therapy, many effects, such as depression and anxiety, may take years and much therapy to overcome. They may never get over it. The stress that many young adults feel from such a restricted diet in childhood literally traumatizes them and that is not something that instantly disappears. You really done and to listen to the voices of PKU patients and their families because restricting access to modern treatments to people who need them just because of their age will be incredibly damaging to generations of PKU patients.
In fact, adults with PKU who are untreated or undertreated effectively have a disability and, under this guidance, would not be being offered fair and equal access to service. The draft Guidance seems to be neither compliant with s13G of the National Health Service Act 2006 nor the Public Sector Equality Duty section 149 of the Equality Act2010.

Finally, I struggle to see how the draft Guidance meets the Government's commitments made in the Department of Health and Social Care's 5 Year Strategy on Rare Diseases which claims to aim to ensure no one gets left behind just because they have a rare disease and that the patients' needs will be put first.
PKU is a rare disease and PKU patients' voices count and they should not be left behind!
We urge you to amend your draft Guidance to make KUVAN available to PKUpatients of all ages.

Name	

Comments on the ACD:

I am writing to express my concerns about the draft Guidance you have issued for Sapropterin/Kuvan for the rare disease, PKU, and would like to submit the following comments:

My experience of PKU has been through a work colleague and now friend of mine who has a son with this rare disease.

Utility Values - 3.14

As an employer, I find it disturbing that you have not taken time, in the past 12 years that Sapropterin has been licenced in this country, to assess how this drug affects the Quality of Life of people living with PKU, including not just patients but their families, friends and employers too.

I would like to give you my perspective on this from my role both as Human Resources Manager and as a friend to someone who's child has PKU.

I have been able to see, over the years, the effect this has had, not only on my friend's son, but on her as a parent, in terms of her own personal well-being and the effect on her career. There was absolutely no doubt that when her child was younger, it was extremely difficult to manage his condition, whilst holding down a responsible job. However, it actually became more difficult as he got older.

When she joined our company, she had just left a job where her manager had made it impossible for her to stay by refusing her "Flexible Working Hours" to look after her son. They insisted she had to be present in the office for the core hours of 9 am - 5.30 pm in [redacted] and would not allow her to condense her hours in order that she could be home by 5.30./6 pm for meal times for her PKU son. Her employers considered that since her child was no longer little (he was in secondary school doing GCSEs), he should be able to do his own meals, despite his complicated dietary therapy and the mental health issues (low moods, anxiety and sleeping problems) that he was experiencing. My friend had to be signed off from work for stress and was ultimately forced out of her job because of her son's PKU disabilities.

When she joined our firm, we offered her flexible working hours which meant that she could continue to work and support her family and look after her son's PKU. However, by that stage, her son was going through very difficult teenage years, he was transitioning from child care services to adult care services (a very tricky time for a PKU adolescent) and his mental health and school attendance was getting worse.

Understandably, it was a very traumatic time for her and her family and sadly, her stress and severe anxiety returned. We reduced her hours even more but eventually, she took the decision to give up work because it was clear that having a child with PKU and the associated disabilities, was not conducive to having a career.

We remain friends to this day and I am close to her son, who I have watched struggle with his condition. It has had a huge impact of his quality of life, from educational, emotional and social aspects. Due to his mental health, he struggles enormously with the strict dietary therapy which led him to being unable to complete his university studies, to cope with independent living, studying and managing his condition without assistance so he is now back home. Even that has an impact on his psychological well-being as it's a constant struggle for him to believe that it is not his fault.

My friend and her son have always talked about how one day Kuvan would be available in this country and that it was likely it would provide him with a better and alternative way of treating his PKU. I was therefore heart-broken for them when I found out that NICE have made the preliminary decision not to prescribe it for anyone over 18.

NICE have not taken into consider that there are many PKU adults out there who are currently untreated or under-treated for a variety of reasons, including disabilities, food intolerances, mental health issues, social or living arrangements, etc. It can only be logical to assume that there would be improvements to the quality of life of these people if they were offered medication, Kuvan, to treat their PKU instead of a complex diet .

For me, the draft Guidance as it stands makes no logical sense. It does not take into account the impact it could have on the quality of life of so many PKU sufferers AND their families and carers like my friend's son and her family; but it also does not take into account the psychological danger it represents to families like my friend's, who will have to continue to battle for their own mental wellbeing, as well as their child's, their child's education, their ability to work and provide for their family and for their child's ability to live independently and provide for themselves in the future.

Another quality of life issue to consider is that some families have more than one PKU sufferer in the household be that siblings or parent/child. For instance, it would be heartless and inhumane to offer a 16 year KUVAN whilst they are doing their GCSEs but force their 18 year old sibling to switch to the diet whilst they are doing their A levels. Or to expect a pregnant mother with PKU who is suffering with morning sickness, acid reflux and extreme fatigue, to treat her condition with a time-consuming, unpalatable PKU diet, whilst she is treating her PKU child with Kuvan. That is twisted.

An even more frightening prospect for these families is when you consider that the recent COVD-19 pandemic is set to cause significant additional demand for mental health care services in this country, especially when our mental health care service in this country is already inadequate and underfunded.

From an employers' perspective, I can only describe the decision to treat children only, as short-sighted as it will undoubtedly be far more expensive to the State in the long-run, in terms of:

- parents giving up, or never returning to work in order to support their older children through secondary school (mostly women as it has been shown in many academic

papers that mothers assume the most part of the burden of care in PKU) (= less income tax and national insurance) ;

- reduced prospects for the young PKU adult due to difficulties attending university/completing education and having lower income prospects (=less income tax/NI);

- young adults brain drain - leaving to go live in one of the other 50 countries world-wide where they will be offered Kuvan/alternative treatments;

- psychological therapies/increased provision of adult mental health care services (both for PKU adult and their families/partners etc.);

- increased need to provide state benefits (such as PIP, ESA) ;

- need for specialised mental health care service within both children's and adult PKU clinics (i.e. dedicated team of psychologists) for the transition period (child to adult) plus for untreated or undertreated adults who are experiencing difficulties.

When our Department of Health and Social Care has issued a 5 Year Strategy on Rare Diseases saying it **"...aims to ensure no one gets left behind just because they have a rare disease",** this Guidance seems to run a mockery of that**. Please amend it so that all PKU sufferers are eligible for this treatment.**

Name	

Comments on the ACD:

The initial news that Kuvan is to become available was met with great relief by us only families who have someone with PKU could understand the difficulties individuals face daily. However, the fact that children from birth will be given Kuvan just to 18 is a very worrying situation. Young people with PKU have to learn to manage a complex low Phe diet with the help and guidance of a doctor, dietician, parents and other supports from family and friends. While all other countries have been providing kuvan to patients for over 11 years in countries that are not as advanced as the UK, NICE only recently put forward this initial proposition to provide kuvan in the UK. The PKU diet is extremely limited and unpalatable no one by choice would eat the prescribe able foods it is done from necessity to stop brain damage, along with a PKU supplement 4 times daily. Children currently grow up knowing the importance of the diet and why they must eat the low protein foods even though they do not like them. I have battled with my daughter to get her to eat the foods and still after 15 ½ years she eats very little pku food and would rather go hungry than eat the majority of PKU foods on prescription. Without parental guidance, supervision,
hours of cooking and preparation daily and constant persuasion she would not take her supplement or eat the low protein foods. As she does not like the food, she uses her 6 exchanges up on normal types of food which are high in protein, this means her only option for food is to then eat the low protein foods that she does not like I have sent my daughter to bed hungry many times and this have a knock-on effect on her mood psychologically and overall wellbeing. The consequences of lack of compliance to a PKU diet, results in out-of-range blood phenylalanine levels poor dietary control leads to brain damage, neurological issues, anxiety, brain fog, memory issues etc. PKU foods do not cook, look or taste like normal foods I can

spend a whole day cooking various PKU foods for them to end up in the bin the following day as she does not like what I have produced. There are no fast foods suitable, no popping to Tesco for a loaf of bread it has to be freshly made always as does all other PKU foods, many items low enough in protein are expensive and only available online so the diet takes lots of planning and organising as does the PKU food prescriptions. Most PKU teens/young adults' rebel against the PKU diet as this is the age that they go out socialising with friends, join university, move away from home or take on their first job. If kuvan was to be taken off people at 18 then there is no way a young person would be able to take on the difficult time-consuming diet at this time of life, it is only as successful as the parent/carer you have throughout childhood as they manage it for you. To eat virtually normally all your life to 18 years then have to transition over to a PKU diet and made to eat low protein foods would be impossible the lifestyle changes and implications on mental health will be huge. Having never coped or managed a PKU diet or eaten the unpalatable foods to go from possibly 15-20 exchanges on kuvan down to 3 without it at 18, along with working, studying, holding down a job or living alone will have a detrimental effect on mental health. High phenylalanine levels will be the end result of not being able to participate in this restrictive diet causing an impact on cognitive function and quality of life. Taking away Kuvan at 18 after living a life of relatively unrestricted eating on kuvan compared to non kuvan treatment is nothing more than cruel. PKU is a diet for life as research has shown so why would you not provide kuvan for life for all PKU patients. It is discriminatory to take away Kuvan from PKU patients who are approaching 18 years after having Kuvan for life and without a doubt cause unnecessary suffering from the drastic life changes and become anxious and depressed. Kuvan if effective allows patents on a very restrictive difficult diet to eat more protein which is amazing but it also has a huge impact on wellbeing and mental health. From personal experience of my daughter taking Kuvan it is life changing not just for her but for us all as a family as it made our daughter happy!

• [redacted] suffers with social isolation and will not leave the house a result of a difficult PKU restrictive diet that is socially unacceptable, she can't eat or drink where her friends can so it's less stressful and less upsetting to stay indoors 24/7. This is not what a healthy 15 year old should be doing PKU has made her a social outcast.

• Stomach upset and heartburn from PKU foods and supplements.
• Struggles to process simple tasks or a sequence of instructions - forgetful.
• Brain fog, headaches lack of concentration cannot process information.
• Extreme mood fluctuations, anger and feeling of frustration/unrest/upset and very emotional.
• Lack of energy.
• Anxiety.
• Constantly left hungry.
• Appointed a psychologist at 14.
• Constant elevated Phe levels – having a detrimental affect

My daughter had a Kuvan trial and was a responder having the required 30% reduction in blood levels. As it was a trial there was no changes made to her diet so she was allowed no more protein exchanges throughout her trail, meaning she had exactly the same diet before, during and after the trial. However, the difference Kuvan made to her mental wellbeing and quality of life was phenomenal. As parents we noticed she was much sharper in her thinking, happier and not depressed as she often becomes for no apparent

reason, not tearful, anxious or angry. Was able to concentrate and take part in school discussions without forgetting what she was doing or talking about, this was reported by class teachers as well as [redacted]. knowing the difference kuvan made to my daughter emotionally, mentally and psychologically plus if she could have more exchanges which when on kuvan long term she would be able to have would make a massive difference to her quality of life. We have tried 3 times via an IPFR to obtain access to kuvan for my daughter, we appointed a solicitor to fight our case to get her kuvan for her and are still going through this process. When my daughter was on the kuvan trial she did it for longer than the normal patient as her levels have and still are very unstable and we could not get a start base line level. So, the actual trial with the drug
was for 7 weeks, we took part in the trial from start to finish for 5 months again due to fluctuation blood phe levels. The process involved my daughter missing school for 3 mornings per week to drive a two-hour round trip for regular blood tests. My husband and myself both had to take time off work 3 mornings per week for the 5-month period, which we were fully prepared to do as our daughter was suffering and it was heart-breaking to see. Taking kuvan daily involved her crushing 14 tablets, mixing with water then drinking with a large glass of water. After this she would have to eat a high fat/calorie breakfast to ensure that the drug would have the chance to work. Then her normal supplement plus a large glass of water straight after. This left her feeling sick every day going to school, taking kuvan is not an easy option and requires dedication and determination. She never complained as she wanted to give kuvan her best shot and did everything by the book thankfully we had the result we longed for. After the kuvan trial had finished I asked my the 14- year-old daughter to write down any benefits she found from taking kuvan so we could show her PKU consultant – ON KUVAN
Happy Easy to string a sentence together
School work was easy
Good memory
Easier to describe feelings
Better reactions
Easier to control emotions
Easier to retain information
Not emotional
Harder to be distracted
Information was processed faster and easier
NOT ON KUVAN
Don’t like PKU foods
Can't determine my feelings
Can't concentrate
Takes a long time to think of words that fit into a sentence
Angry
Hyper sensitive
Bad reactions
Anxiety
Can't retain information
Brain fog
Very easily distracted
Spaced out
Unable to follow simple instructions
Can't process information
Feel like I'm watching my life not being part of it
Can only follow 1 simple instruction when told multiple
Terrible organisational skills.

To live hating the way you feel daily in a state of constant upset, anger, feeling overwhelmed, angry, emotional, frustrated, tearful, lacking in confidence, forgetful, hungry, frightened, anxious, social difficulties, psychological problems plus having to eat food you do not like and that makes you feel ill is a massive struggle for my daughter. She should be doing normal teenage girl things going to the cinema, McDonalds, for a coffee or a milkshake with her friends instead she lives struggling in a very unhappy life which is totally unnecessary when Kuvan changed her and her life making her feel “normal”. The worry of prolonged elevated levels is reduced on kuvan as it results in good control of Phe levels. My daughter has been required to see a psychologist which caused her a great deal of distress to deal with PKU when numerous studies have been made about Neurobehavioral/neuropsychological problems in PKU patients and how kuvan in my daughters' words was all she needed to feel mentally well. The key to reducing risks associated with PKU is good metabolic control for life something Kuvan plays a huge part in allowing a much better quality of life.
While my daughter was on the kuvan trial she was initially started on a 10mg dose which for her did not reduce her blood Phe levels so she was increased to 20 mg of kuvan this was the dose that showed that she responded to kuvan, and after speaking with her metabolic specialist we were informed that she has the 30% reduction which is whats required to be classed as a kuvan responder. Therefore, if my daughter was to get kuvan when it is made available after NICE has approved it for children then even though we know kuvan works for her it would have little or no effect on her as the dose is too low. So, my daughter has experienced the life-changing benefits of kuvan and it going to be available but not at the correct dosage. This could be the case for many children they will respond to kuvan but will not be able to benefit as the correct dosage is not being made available by NICE/NHS England. BioMarin actually state if the kuvan dose at 10mg does not work then the dose should be increased to 20mg, so you are not providing the recommended and correct effective dose denying people of a decent quality of life. I'm sure you would not give a diabetic half the dose of insulin!! The impact of PKU travels further than the child or adult with PKU, as a family we have had a huge strain on our relationship both myself and my husband have suffered depression, stress and anxiety as a result of living with a difficult to manage rare disease and supporting our daughter through the process of dealing with the issues PKU presents. We are unable to share the management of PKU and my daughter has never slept out or stayed with anyone other than the two of us parents due to her restrictive diet as all her food is freshly prepared, weighed, measured, ingredients of everything checked and re weighed and recalculated if any food is left on the plate. We have stopped going out with family and friends and now stopped going on holiday abroad as it is very difficult for my daughter to sit and watch people eating foods she cannot have and there is not always a suitable alternative or option for her to have causing her to be upset. While on holiday there is plenty of food in restaurants but very little suitable for her to eat. She has had to watch children
in parties eat food while she can't have anything, be disappointed and embarrassed as restaurants refuse to make her food she can eat and this all has an impact on her and as a result avoids all social situations both individually and as a family.
The decision to exclude women of childbearing age from receiving Kuvan is absolutely appalling, pregnancy for PKU women requires an even stricter diet than young children with fully developing brains. To expect a pregnant woman to manage on 1 or 0 exchanges which is what pregnant ladies will have to do to protect the growing foetus from the detrimental birth defects that PKU causes the unborn baby is unbelievable when kuvan will make a huge difference, instead of worrying the whole way through pregnancy being unable to eat so many basic

foods when kuvan would allow women by controlling phe levels to have a worry free less stressful and enjoyable pregnancy, by protecting both the baby's brain from unnecessary and preventable brain damage along with protecting the mothers mental health. Maternal PKU syndrome can cause intellectual disabilities, microcephaly, heart defects, facial deformities, growth abnormalities, low birthweight a clearly worrying time for a PKU mother. To refuse kuvan to pregnant women leaves them with mental and psychological issues.
My daughter would like to go on to further education if she was to have good metabolic control which is what she had on kuvan this could be acheiveable. If she was to have kuvan it would help her think clearer, improve concentration, mood, anxiety levels, focus, organisational skills, reaction and thinking times are more responsive plus the actual food in the pku diet is less restrictive and easier to manage with kuvan allowing more protein exchanges. As parents we do not want to hold our daughter back when she has clear goals and dreams but her life success is being determined by whether she can access kuvan for life not just the next two years until she's 18. Pku is a lifelong condition that should be managed and treated for life with the most adequate and effective treatments, kuvan is now an old treatment for PKU and there are many new treatments available, why is the UK so behind in PKU treatments compared to
many other countries some of which are not as advanced as the UK.
We would be grateful if you take time to read our statement and hope you change your minds in allowing Kuvan access for all PKU patients we appreciate it's hard to understand the difficulties PKU patients suffer with daily but please take our word and understand it was a life changing experience seeing our daughter happy and contented instead of not being able to take part in life.
Thank you for reading

Name	
Comments on the ACD:	
I find life with PKU difficult to follow, I've had pku all my life and I've always struggled. From leaving primary school I began eating what I wanted because I began to have the freedom I didn't have beforehand and I reached an age where nobody could tell me I couldn't. I found secondary school very difficult because I would find myself watching clouds and looking out of the window whenever I had high blood levels and a few years ago I found myself feeling anxiety to the extent of locking myself indoors and refusing to speak to anyone. I was actually diagnosed with extreme anxiety. After leaving school I became scared of things which people usually wouldn't be scared of, like loud noises, confrontations, and crowds of people. I was planning to do a level 2 football course after school, but I had a lot of hospital appointments to help with my anxiety and the coach (an ex military guy with a ridiculously loud voice) refused any time off for appointments. That felt like confrontation to me and I really am scared by strong, loud personalities. I left that football course the very next day and began attending a group where I was put among people with learning difficulties. We were learning cookery, IT, English, and maths, and (for once) it felt like a luxury not to have any confrontations or egos to deal with. It was a group of happy people getting on with what we were learning. I find being off diet is a bad thing.	

Sticking to the pku diet is definitely the most challenging thing for me. When I was younger it has hard watching everyone around me eating things I shouldn't be eating always creates temptations, like when they're eating
chicken burgers and things while I'm eating PKU pasta I just felt like abandoning the pasta and taking the burgers off them.

But now I'm older and have been off diet for a while, whenever I try my best (with the help of my family) to get back on diet it is very difficult. Not so much because of the food, but because of crashing headaches and bone pains.

When my levels are high I find myself getting crushing headaches, I have difficulty understanding things I would usually understand perfectly well, and if I'd done something wrong I often can't understand what I've done. I feel a decline in self-belief and find myself not wanting to move or do anything, with words going through my mind like, "Why bother? I haven't got the thoughts or insights to make a difference anyway. Having high phenylalanine levels isn't a nice feeling, that's for sure!

My concentration was impacted at school and any speaking activities I couldn't manage at all due to the PKU 'brain fog' obstructing what I had to say, and I really wouldn't know what to say without putting myself in a situation of possible ridicule. I am unable to work and I receive enhanced pips for care and mobility. My parents look after me and so does my grandma. My hand tremors are so bad that I can't hold a pencil or pour a drink into a cup without the water going everywhere. I take tablets for my mental health. I have brain damage which was found by a scan.

I'm stuck with PKU and I can't get rid of it. Being given a treatment that would help me live a more normal life would mean the world to me and my family. I may be able to find the confident person I was before the NHS advised me to stop the dietary therapy.

I was advised to stop my pku treatment at 15, with no backup plan or any other options to help with my health needs. Giving children kuvan and then taking it away is not much difference in years to when I was advised to stop the pku diet. I've not been able to get back on track. With my experience in mind, how would it be possible for children to stop Kuvan treatment at 18?

Name	
Comments on the ACD:	

NSPKU is concerned that the draft NICE decision is not correct and needs changing:

1. We welcome the recommendation that children can use Kuvan but NSPKU believes that patients of all ages with PKU who respond to treatment with Kuvan should be able to use this medicine.
2. NICE has not considered the problem about young people stopping treatment with Kuvan on their 18th birthday. Managing your phenylalanine levels with dietary treatment alone is very difficult, especially for teenagers. 18 year olds accustomed to a very relaxed diet through using KUVAN will not have the coping skills to switch to a strict diet. NICE has ignored this issue completely.
3. NICE's analysis underestimates the benefits of KUVAN treatment for adults with PKU. They say there is no risk of permanent damage to the brain after the age of 18, but this is contradicted by other statements made by NICE which recognise that permanent harm can occur after the age of 18. NSPKU also recognise that many adults with PKU have very serious symptoms caused by high phenylalanine levels in adulthood. These problems in adults are undervalued by NICE.
4. NICE has not considered the harm of Maternal PKU syndrome and the worry this can cause to women with PKU. When deciding that Kuvan is not cost effective in adults, NICE has ignored the benefits to women of using Kuvan to help women with PKU have safe and happy pregnancies. NICE has recognised that controlling phe levels is important in early pregnancy, ideally before conception, and has recognised that this would reduce the risks of Maternal PKU syndrome. However the harms from high levels in early pregnancy have not been included in their cost analysis. NSPKU believes that NICE has failed to take account of the issues experienced by women with PKU and that this is a major failing in their draft guidance.
5. NICE has ignored that many adults with PKU who have problems associated with high phenylalanine levels – like brain fog, depression or poor memory – simply cannot cope with dietary treatment. The NHS should not leave people without a realistic option for treatment. NSPKU also believes that NICE has undervalued the work and impact that managing PKU can have on adults with PKU and their families.
6. People with learning disabilities are at a higher risk of being unable to control their phenylalanine levels with dietary treatment. The need for help with dietary treatment might also restrict the independence of people with learning difficulties. NICE recognised that people with learning difficulties might struggle with dietary treatment but there is no evidence that this has been included in the cost analysis.
7. NICE has recommended using KUVAN at a dose of 10mg/kg. NSPKU agrees that clinicians in the UK will prescribe more efficiently than in the US and that an average dose of 10mg/kg is appropriate for the cost analysis. However NSPKU believes that clinicians should be able to prescribe within the marketing authorisation, which ranges from 5mg/kg to 20mg/kg.

Name	
Comments on the ACD:	

To whom it may concern.
We are parents to a 17 year old boy with PKU, he will be 18 in May.
It was the hardest day, our world came crumbling down around us on the day our son was diagnosed with Phenylketonuria. This was a metabolic condition that ourselves and no one around us had heard of. Sitting in the hospital with our baby having him go through numerous blood tests, listening to a mountain of information about something we knew absolutely nothing about was certainly overwhelming to say the least. Weeks, months and years past and we were learning, not only to be new parents but to be parents to a child with an extremely rare condition. We could not have done any of this without support. Support from medical professionals, speaking to other families, physical and emotional support from family and friends played an integral part into helping us through difficult times. Our son was and still is amazing but he has certainly faced difficulties with regards to his PKU over his 17 years. The upset he faced when having to sit alone to take his supplement in the school hall, a cooking day that he was made to sit and watch his friends take part in as no one had thought to inform us of this so he could be catered for. Nor had they thought to find out that actually he was able to partake in this activity with his friends, he was just unable to eat it. The upset and embarrassment to my son on the rare occasion of going to restaurants on a whim and finding out they had nothing suitable for him to eat, their unwillingness to cater a simple meal for him or the utter disgust and roll of their eyes that you had even asked. The day he broke his heart at the restaurant table because they were too busy to make him vegetable gravy and wouldn't allow me to bring our own to put on his lunch. He, as a young boy apologised for being such a burden to everyone. This was and still is, as heart breaking as it was the day it happened. There are many more examples. He has also struggled throughout school academically with regards to his PKU. He would also avoid having to acknowledge PKU, avoided talking about it to his friends, this in itself meaning he would hold on to his feelings. This would at some point lead to an emotional outburst, lots of shouting, anger and tears. This was and still is exhausting, not only for himself but for all his immediate family. He has a younger sister and brother and this is very upsetting for them to witness or to have this upset and frustration directed at them. These outburst still happen, only now they are more angry, happen more often and have hormones thrown in the mix too. Our son, as much as he loves and adores his siblings definitely holds some envy towards the fact they don't have PKU. This makes him feel guilt and upset for even having these feelings.
Roll on to the last couple of years and my son is currently at sixth form studying Business and ICT. He has been offered places at numerous universities to study Politics.
Our son is currently struggling with regards to his diet, the sheer volume of tablets he takes per day (he takes 75 at the moment) to allow him his 6/7 exchanges per day and this is becoming a bone of contention. He is not a boy but certainly not a man and needs our support more than ever to make sure he sticks to his diet for life, to help him fulfil his dreams of university and politics. He will need support to be able to look after his prescriptions, cook for himself, shop for food for himself, store his foods and medication, change GP's and hospitals, how to deal with GP's and receptionists, taking bloods regularly and posting these to hospital. Adapting his exchanges depending on his results, weighing his exchanges. All of this whilst learning to study independently, live independently, clean, look after himself, socialise and adapt to the change of moving from home for the very first time. This is daunting for anyone and even more so if you have a medical condition that requires a lot of work to keep on track so that your PHE levels stay in a range that is safe. Coming off diet and then maintaining the ability to not be affected by this

and continue to study and fulfil his dreams makes for a difficult task on top of everything else an 18 year old boy has to go through.
For NICE to say there is no risk of irreversible brain damage to adults is inconceivable. The human brain is more complex than any other known structure in the universe. I am overjoyed at the decision for Kuvan to under 18s. However I find it completely discriminating at the very least that over 18s, or once they become 18 will not be eligible to a drug that will allow sufferers of PKU the help they clearly would benefit from to maintain their diet for life. Coming off diet certainly would be more of a burden to the NHS. The fact that Kuvan is widely available around the world is astounding. I know of others who struggled when they came off diet, mentally, emotionally and physically with little or no support. They need support not dismissal.

Thank you
A mum of a 17 year old boy with PKU.

Name	
Comments on the ACD:	
Dear nice team, What can I say: A lot really but it would take forever, Why can't adults have access to Kuvan ? My daughter was born in 1976 , the diet is horrendous and in 1976 the food supplements were atrocious and quite disgusting, it was literally a diet of fruit and veg, monthly blood taken out of babies neck , always hungry children , birthdays an apple with a candle in , I could go on and on . Please let these adults who have suffered all there life have some enjoyment , can you imagine being able to eat protein without weighing and counting , I would love the people who say no to the drug just for a day , yes a day go on this diet and then imagine it for life !!! This decision is appalling and cruel , what is the point of research if it's only the chosen few who can have it . From a very dissatisfied and disappointed mum. Kind regards	

Name	
Comments on the ACD:	
I would like to strongly advise that adults as well as those under 18 yrs should be given the chance to live a normal life with the drug Kuvan. Those with PKU have lived a stressful life as children and young adults doing their best to regulate their lives. It is the right of every person to benefit from wonderful research and advances in science. In these modern times we must not discriminate against people on the basis of age or anything else.	

Name	
Comments on the ACD:	

I write to you today with regards the forthcoming decision of providing sapropterin dihydrochloride to those with PKU, and note the current draft is to recommend only to children and not adults. I think now is the time to be candid with my response as I believe with all due respect the decision is short sighted. Here are some emails I've recently sent on the matter, I hope you will read them through.

1) To Chair of NHSPKU
Further to my earlier email, suggesting a scientific advisory panel in addition to a medical advisory panel, something which I forgot to mention yesterday, was where has this arbitary age of 18 come from? People might be able to vote at 18, and tecnically become an adult, but from a physiological point of view, what is so special about age 18 in the context of sapropterin and PKU, is there some study which proves there is only benefit up to 18? To be honest, if its true, "It is uncertain how well it works because there is only short-term clinical trial evidence. There is no clinical trial or registry evidence to show whether sapropterin reduces the need for a protein-restricted diet or how it affects quality of life." that as mentioned yesterday why aren't we going for funding to start a clinical trial to get the data to prove it works in adults? Does NICE have enough data to justify recommending it to children? Just because children on average have a mass ("weigh less") than adults and so need less KUVAN doesnt seem a good enough justification to give it to chidren and adults. This is just a bizaar, illogical, non-scientific approach. I think NICE need to be told this. They make the statement, there isnt' irreversible brain damage in adults with PKU, how much data and published papers do they have to make that conclusion. I would be extremely weary of making such a Message sentstatement. It would be like saying, if you gave a child lots of alcohol, and then the same to an adult, only irreversible damage would take place in a child not and adult, which I believe is not true. Do you have a list of all the people who at NICE will be making the decision? I think its time for me to start speaking and canvassing them. If the government gave me 10 million, and a team was assembled, we could solve PKU, its not even about the money, just the time, lab resources and dedication to do it.

2) To Matt Hancock:

I'm not sure if you remember me and I know at the moment you are very busy with COVID-19, congratulations however with the vaccine rollout, it really shows what can be done when we put our minds to it. On that note, can you do something about KUVAN/Sapropterin. As you may/may not know there a draft NICE draft guidance recommends sapropterin for children with rare inherited metabolic condition phenylketonuria | News and features | News | NICE recommending Sapropterin, only is given to children up to aged 18. NICE cite lack of evidence to support its role and adults and cost. These reasons dont really hold true, almost of Europe provide Sapropterin to all ages, as does Canada and Australia. The numbers are low about 1 in 10,000 have PKU and only about 25% respond to Sapropterin. Can you imagine your diet being more strigent, that a Vegan diet, in which even if you were on a Vegan diet you would see have to avoid anything with a high protein content, e.g. nuts, beans, pulses etc etc. and consume numerous powered sachets each time containing every amino acid except phenyalanine, which because it cannot be broken down my PKU patients, if consumed if toxic to

the brain, and as we know effect brain developed at all ages. As we now know from UK neuroscience research that the brain continues to develop into adult hood. We the new setup of DNA sequencing for COVID-19, this resource could now easily screen all PKU patients, and be used to build up a complete database of all mutations, which could be correlated to those who respond to KUVAN, thus saving the NHS money in the long term. It would also unlock the potential of thousands of people, to live a more normally and get the protein nutrition that would benefit their brain development and thus potential. Please would you therefore consider having a word with you colleagues at NICE and Committe A who I believe are making the decision. Could you confirm receipt of this email, just so I know it reached your office? I've copied this email to a few people at NSPKU - National Society for Phenylketonuria.

I don't have PKU, but know someone who is. Without in any way sounding condescending believe that if they could have a more balanced diet including Phenyalanine, their intelligence would increase, and be more similar to mine. I also truly behaviour the role of phenylalanine being required in the body as a dietary amino acid has been overlooked. Although we do metabolise it to tryptophan, hence the supplements those with PKU contain tryptophan and not phenylanine.

NSPKU have urged people to talk about their life experiences of PKU as an adult.

I think what really needs to be considered, that if a "normal" diet with more protein in it, but also all the micronutrients associated with a more freely available diet, if this impacts the brain function on those with PKU, can any price be put on the potential of a human brain, if there is something with is available which can improve it, in the same way education in the UK is now universal and available to all? I think the amount it will cost, is small in comparison to the overall benefit, even in hard UK tax returns from the PKU patients increase in salaries, through better jobs, from being on KUVAN etc will produce.

Please can you forward on my behalf this message to all members of committe A
Committee A members | Technology appraisal committee | Meetings in public | Get involved | NICE

Name	
Comments on the ACD:	
I belive truly that kuvan should be for everybody with pku not just for the under 18s also for the adults. Thank u	

Name	
Comments on the ACD:	

Dear TA Team 1,

I welcome the recommendation that children can use Kuvan, but I believe that patients of all ages with PKU who respond to treatment with Kuvan should be able to use this medicine. I am writing as a friend of an adult with PKU, an individual whose kindness, maturity and sound advice has enriched the lives of myself and many others. Indeed, when I was taken into hospital for an emergency hernia operation, she was the only one of my friends who came to visit me. Whilst she has achieved great success in both her education (completing a PhD) and employment, living a full and fairly happy life, it has not been without considerable sacrifices. It is only through the most rigorous self-discipline that she has been able to live as she has, something which has often caused her to be distanced from those around her, making it hard to form relationships and resulting in a lot of day-to-day stress. Kuvan would offer her and other adults who suffer the same condition a chance to transform their lives for the better, and I cannot see why this opportunity should be withheld.

NICE has not considered the problem of young people stopping treatment with Kuvan on their 18th birthday. Managing phenylalanine levels with dietary treatment alone is very difficult, especially for teenagers leaving home, starting work, and establishing themselves as adults in the world. 18 year-olds accustomed to a very relaxed diet through using KUVAN will not have the coping skills to switch to a strict diet which involves constant preparation of meals, precise measurement of all foods, constant management of prescriptions, regular self-administered blood tests, and difficulties in participating in social occasions based around food, including eating out in restaurants. It will lead to people not continuing the diet, being lost to treatment and having health issues related to high phenylalanine levels in adulthood. NICE has ignored this issue completely.

NICE's analysis underestimates the benefits of KUVAN treatment for adults with PKU. NICE says there is no risk of permanent damage to the brain after the age of 18, but this is contradicted by other statements made by NICE in the document which recognise that permanent harm can occur after the age of 18 and that brain development continues until age 25. There is good evidence that many adults with PKU have very serious symptoms caused by high phenylalanine levels in adulthood. These problems in adults are undervalued by NICE. Furthermore, new research into neuroplasticity and more recently neurogenesis is showing more clearly that the brain continues to change and develop throughout life. NICE has ignored that the adult brain does not stop changing and developing.

NICE has not considered the harm of Maternal PKU Syndrome and the worry this can cause to women with PKU throughout their lives until the menopause. When deciding that Kuvan is not cost effective in adults, NICE has ignored the benefits to women with PKU of using Kuvan to help them have happy intimate relationships without having to worry about an unplanned pregnancy resulting in Maternal PKU Syndrome, and have safe and happy pregnancies, whether planned or not. NICE has recognised that controlling phe levels is important in early pregnancy, ideally before conception, and has recognised that this would reduce the risks of Maternal PKU Syndrome. However, the harms to mother and child from high levels in early pregnancy have not been included in the cost analysis. The mental and physical experiences of women with PKU who have gone through the pre-conception diet and a pregnancy, a time when hormonal changes and other health changes due to

pregnancy are significant, have not been taken into account. Pregnancy can also result in severe illness that makes the diet even more difficult both mentally and physically. All of these difficulties and more are articulated by PKU patients in Ford, O'Driscoll, and MacDonald, 'Reproductive Experience of Women Living with PKU', Molecular Genetics and Metabolism Reports 17 (2018), pp.64-68, which NICE needs to take into account. The hormonal changes experienced by women during the menopause should also be taken into account as more early treated adults go into middle age: women need help to ensure they can maintain low phenylalanine levels throughout life. I believe that NICE has failed to take account of the issues experienced by women with PKU and that this is a major failing in the draft guidance.

NICE has ignored that many adults with PKU who have problems associated with high phenylalanine levels – like brain fog, depression, or poor memory – simply cannot cope with dietary treatment. The NHS should not leave people without a realistic option for treatment. Also, many adults who experience difficulties were told by the NHS when they were children in the 1970s-1990s that they did not need to continue the diet in their late teenage years and in adulthood, and so didn't, trusting their clinicians. The NICE draft guidance does not take into account that they were advised in this way, and that Kuvan would help them control their phenylalanine levels.

I also believe that NICE has undervalued the work and impact that managing PKU can have on adults with PKU and their families. People with PKU spend a lot of time looking after themselves and controlling their diet, or suffering the symptoms of high phenylalanine levels. This is clear from studies such as Ford, O'Driscoll, and MacDonald, 'Living with Phenylketonuria: Lessons from the PKU Community', Molecular Genetics and Metabolism Reports 17 (2018) pp.57-63 which gives a detailed account of the lived experiences of people with PKU. Also, the draft guidance does not take into account the positive economic, health, and social impacts of having more people working and achieving more in their careers, contributing to their communities, and being more active members of society, all of which would be possible with their phenylalanine levels better controlled through the use of Kuvan and any other new treatments that are created to treat PKU.

People with learning disabilities are at a higher risk of being unable to control their phenylalanine levels with dietary treatment. The need for help with dietary treatment might also restrict the independence of people with learning difficulties. NICE recognised that people with learning difficulties might struggle with dietary treatment but there is no evidence that this has been included in the cost analysis in this consultation document.

NICE has recommended using KUVAN at a dose of 10mg/kg. I agree that clinicians in the UK will prescribe more efficiently than in the US and that an average dose of 10mg/kg is appropriate for the cost analysis. However, I believe that clinicians should be able to prescribe within the marketing authorisation, which ranges from 5mg/kg to 20mg/kg.

I believe that all people with PKU should have access to Kuvan on the NHS, and all future treatments for PKU that become available should also be funded to enable people with PKU to live freer, happier lives.

Yours faithfully,

Name	
Conflict	
Comments on the ACD:	

I am writing with regards to the draft Guidance you have issued for Sapropterin/Kuvanfor the rare disease, PKU, and would like to submit the following comments to express my concerns :
Your appraisal says: “there is no extra increase in quality of life for adults tooffset these costs” This makes no logical sense. How can there not be an increase in quality of life for adults by changing from an onerous, expensive, unpalatable, unsociable, complicated, time-consuming, life-restricting dietary therapy to a simple pharmaceutical therapy which offers the chance of a near normal diet and nearer to normal life? It also does not make sense why you assume that the quality of life of an currently untreated or undertreated PKU adult, who is living with damaging effects on their brain because they cannot adhere to the diet, would not be improved by having access to an alternative treatment to a diet.
Our personal story with regards to quality of life is as follows:
My son was diagnosed with PKU by the heel prick test when he was born in 1998 and was under the care of Great Ormond Street Hospital (GOSH) throughout his childhood.
As you know, transition from child care service to adult care services is normally expected to start around the age of 16.
However, at the start of his teenage years, my son began to experience issues with his mental health (sleeplessness, anxiety, lack of confidence and self-esteem, loss of organisation skills, aggressivity, low moods, school refusal - possibly triggered by severe bullying for reasons associated with his PKU). As he grew older, I had less lose control,

as a parent, on his adherence to dietary therapy and, despite firm encouragement and lots of education about his condition as he was growing up, he began to veer off the PKU diet. This was a source of extreme worry and anxiety to us as a whole family. My son was referred to CAMSH and a psychiatrist. He stayed at home to study and had some private tutoring but his education suffered enormously, This was not helped by the fact that his school was not supportive and did not understand his condition, deeming his behaviours to be deliberately bad and implying that there were issues with my parenting. The dreadful vicious circle of mental health issues and non-adherance to diet then ensued - this vicious circle in PKU patients is well documented so I will not repeat I there.
GOSH was not therefore willing to start his transition to adult care services at 16, seeing that he was not psychologically ready. In fact, they kept him at GOSH until the age of 181/2 , at which point, he was abruptly and unceremoniously transferred over to UCLH, with very little in the way of “transition”.
Transitioning from the children’s hospital he had known all his life to adult care services at UCLH was a shock and an extremely difficult time in his life. He failed to attend several PKU clinics, either through the forgetfuless caused by his PKU or his refusal to attend [reasoning impairment due to PKU]. He lost letters. Missed phone calls. Rejected help from me. He struggled through his A levels and attended university, but managing tertiary level education, time-keeping, setting up a new GP, struggling to get his reluctant GP to understand his condition and prescribe his products, managing his complex, time-consuming, unattractive diet, liaising with pharmacists, collecting his prescriptions, chasing up missing products, not being able to join in “socials” and blendin with his peers - all got the better of

him. The burden of PKU is huge and far-reaching and I believe this is well documented in the Committee papers. Furthermore, having been bullied for “being different” at school, he envisaged university as giveing himself a chance of a “fresh start” but in fact, his PKU inhibited him once more from living his what should have been the best years of his life. It all fell disastrously to pieces. He dropped out of university in both years 1 and 2, and despite several attempts, ended up moving back home and giving up any hope of completing a degree. The mental health issues caused by his non-adherence to PKU diet have included severe depressive episodes, anxiety, body dismorphia, disordered eating (including starvation) and social withdrawal.

My son was first told about KUVAN when he was about 8 or 9, He was 10 when it got licensed in the UK. Each and every clinic he attended, we always asked about it and were always promised it was on its way. My son was advised that it would be very likely that, if he was a responder, he could eat an almost normal diet - his hope and dream! He has waited 12 years and now, he finds out that the draft Guidance excludes him from the opportunity of finding out if KUVAN could change his life because there is not enough evidence that it would make a cost-effective improvement to his quality of life. Your press release states that adults with PKU might find your decision “disappointing”:how dare you be so condescending? My son has waited in vain for 12 years to try this medication and knows that his teenage years, his secondary and university education,

his mental health, his eating habits/gut health and start of his adult life might have been very different had you approved this medication sooner. His quality of life matters! AllPKU lives matter! My son is now 22 and struggling to turn things around. He finds it extremely difficult to adhere to the dietary therapy and it is not a lifestyle choice he has any control over, and as such, he remains one of the many “under-treated” or“untreated” PKU patients in the UK - effectively saving the NHS a lot of money. It is awarped view to discard adults’ eligibility for a quality of life-changing medication, when the NHS saves money every single day on patients like my son, to whom you offer no support, no alternative treatment and no hope!

So, clearly, PKU affect my son’s quality of life and health, but please note, it also has affected the whole family. As a “PKU mum”, I ended up giving up my career (and good income) as the strain of holding down a job and parenting a young person with PKU with mental health issues was too much to bear. During this period, I was even subjected to discrimination at work and refused flexible working hours to accommodate my need to be present for my son’s dinner time and was effectively constructively dismissed. My employers did not understand that it is not just mothers of young children that need flexibility for their carer duties and that people with PKU might have care needs throughout their lives, not just when they are little. And even when I found a job with understanding employers, my own mental health was so badly affected by my son’s issues that I was signed off for stress several times and came to the conclusion that full-time work was impossible when one had a child with PKU and associated mental health issues. PKU is a rare disease that often attracts little sympathy. It involves a “diet” (most people are on some sort of diet these days and there is very little understanding [aka no idea]of how impactful the PKU diet is on quality of life of the patient and their carers), there is no visible disability and mental health issues, despite all the campaigning, are still very much a taboo and misunderstood matter.

It is also heart-breaking that in order to get a better quality of life, young PKU adults like my son, will consider moving abroad to live in one of the other 50 countries world-wide where they will be offered Kuvan/alternative treatments.

So, would having access to Kuvan increased the quality of life of my son and his family -YES 100%

Your appraisal says:“ There is also no risk of irreversible brain damage in adults with PKU”.
I can only hope that you will thoroughly review this statement at your review meeting on7th April 2021 as it is an astonishingly bad interpretation of the evidence and contradicts what it written further on within the appraisal document: ”...adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25." .

In my opinion, it would be irresponsible, unethical and dangerous to enforce a change of therapy from pharmaceutical to dietary at the age of 18 from a quality of life perspective but also from a physical aspect:
Permanent psychological damage
NICE has a public duty of care to listen to people with this rare disease. It is not simply a case of of reading academic papers and studying charts and graphs. The people behind this disease are very real. You must get into the psyche of this disease. It’s not “just a diet”. You must not underestimate the enormity of the scale of effect this disease has on people. The brain damage lurks, insidiously and invisibly, in their lives and many suffer in silence or are met with disbelief or with a lack of understanding from their GPs or consultants. From personal experience, the effects of the brain damage that my son has suffered every day since he turned the age of 18 are not reversible. He will never regaina chance to perform as well he could have done at school, he will never regain those heady years of university, getting a degree and making friends for life, he will never get that chance again to start his working life as a confident, well-adjusted graduate, he may have years and years of expensive talking therapies to deal with his depression, anxiety and lack of self-esteem, restricted growth and poor eating habits as a result of his disordered eating, but the issues are deep-rooted and won’t be reversed by simply returning to strict dietary therapy. The damage is done. The NHS cannot undo the past and reverse the damage caused to him.....but the NHS must prevent permanent psychological damage to other young people with PKU by:
- not putting a teenager through the psychological torture of preparing to change therapy from medication to diet in the years leading up to their 18th birthday; and
- not taking away Kuvan from a person on their 18th birthday when they are still in education or about to start an apprenticeship or their first job.
Brain development beyond 18 yrs
There is plenty of academic research out there which shows that the brain continues to develop beyond the age of 18 years of age. It is widely believed that not ony does the brain develop well into our mid-twenties, but may continue up to age 30 years. This is supported by neuroimaging research. For example, the frontal lobes, home to key components of the neural circuitry underlying “executive functions”, are the last areas of the brain to mature and may not be fully developed until halfway through the third decade of life (Sowell et al 92). Even your draft Guidance accepts that “adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25.”
Going back only 30/40 years ago, the NHS deemed that it was safe for children as young as 8 years old to come off diet without risk to their brain. We now know this was wrong. Back then, we did not have the foresight that we have now. We now know that
we do not know everything there is to know about the human brain. The human brain is more complex than any other known structure in the universe. It is therefore inconceivable for NICE to conclude that there is no risk of irreversible brain damage to adults with PKU.

There is still lots yet to learn about the long-term impacts of PKU on the human brain and indeed, on the body, the gut biome system and it would be immoral and irresponsible of our healthcare system to assume that there are no risks of long term issues in patients with PKU.
My son is one of many PKU adults who struggles or cannot adhere to the dietary therapy, through no fault of their own. It is very concerning that the NICE committee has failed to understand or address why dietary therapy may not work for for all PKU adults. Moreover, it would be highly unethical of the Department of Health and Socia lCare in this country to refuse to offer these patients an existing alternative treatment to diet, whilst allowing them to remain untreated or undertreated, with ongoing damage to their brains and no support or options to improve their health.
NB PKU patients over 18 may not be successfully treated by diet for many reasons, including:
- Lack of inhibitory control. In order for a PKU adult to eat healthily and chose low protein foods over “forbidden” foods, they need the part of their brain that controls their impulses to function properly, otherwise they make a poor choice. ;for a person with PKU to make the right food choices, they need to have the ability to inhibit their impulses. [Higgs, S. (2016)].
- Effect of childhood trauma from being subjected to such a restricted diet as a child causing physical and mental aversion to the diet.
- Gut issues or food intolerances
- Traumatic life events or changes. Example: a friend of mine with PKU was told by her metabolic team to come off diet when she was going through a particularly harrowing time (family bereavement and marriage breakdown) as the diet would be too hard for her to cope with under such circumstances.
- Living arrangements (PKU diets involve cooking from scratch, require cooking facilities and ample storage - not always possible if you live in small or shared accommodation, are without cooking facilities etc)
- Mental health and other disabilities
- Illness, hospitalisation or pregnancy which affect appetite.
HUMAN RIGHTS & DISCRIMINATION
Your appraisal asks: “Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?”
Yes, there are. The draft Guidance proposes to stop the provision of Kuvan on a patient’s 18th birthday, with no consideration to how this discriminates on patients over the age of 18, on several grounds, including their gender, their disabilitiy, their age and pregnancy and maternity, or how ethical it is.
The NHS is required to have regard to the need to eliminate inequalities of provision of care under section 13G of the National Health Service Act 2006 (NHSA) and is also subject to Section 147 - Public Sector Equality Duty of the Equality Act 2010, to ensure that the human rights
The European Guidelines for the Treatment of PKU (EGTPKU) stipulates that PKU patients of all ages require of treatment for life. It is therefore discriminatory again stage and goes against the recommendations of the EGTPKU to restrict access to Kuvan to PKU patients under 18 years and refuse access to the only other treatment for PKU available in the UK, to PKU patients over the age of 18.
PKU women planning a family or pregnant suffer unspeakable stress and strain during the pre-conception and ante natal periods, as well as post-natal, coping with their own health plus concern for their baby and the dreadful, horrific consequences of high PHE levels. It is discriminatory against maternity and pregnancy to not offer an alternative treatment to PKU adult females over the age

of 18 who cannot adhere to diet or for whom KUVAN would improve quality of life during their child-bearing experience.
It is discriminatory against disability not to offer an alternative treatment to diet to adults with PKU because they are struggle with or unable to manage the dietary treatment because of their disability.
It is discriminatory against gender to not consider the quality of life of the carers of people with PKU, which is a life-long committment and an heavy burden of care which, as has been shown in studies, mainly falls on the mother, and it is the mother who often has to give up her career and income to care for their PKU child.
It is also unethical to restrict a person with PKU's career choice by not offering them access to a pharmaceutical treatment which would allow them to freely chose their career, eg enter the armed forces. Instead, they face restrictions in their career choice because the only option available to them is dietary therapy which is not compatible with all career choices.
Would it be an ethical situation to have a family with two children with PKU (eg a 15year old studying for GSCE and an 18 year old doing A levels) and the carer (usually the mother) managing the two siblings mental health implications whilst giving them two different therapies - one takes simple medication and the other a complicated diet ?
Would it be ethical to have a PKU woman who is already a mother to PKU offspring -struggling with her own dietary therapy during pregnancy whilst giving Kuvan to her PKU offspring?
INCOMPLETE GUIDANCE ON TRANSITION CHILD-ADULT CARE
Your appraisal asks: "Are the recommendations sound and a suitable basis for guidance to the NHS"
The draft Guidance does not consider or provide any guidance to the NHS as to how treatment would be stopped in practice, how the NHS would implement the re-introduction of the ultra harsh low protein diet to a patient who has not grown up with the diet and has no "taste" for it.
It is not stated whether the transition would take place in child or adult care services and no costings for additional services have been factored into NICE's cost analysis. NB Children's clinics have purpose-built kitchens to teach the children to cook PKU recipes from a young age and demonstrate new products and recipes. Most adult PKU clinics are an add-on to another department and don't have the necessary facilities for dietary therapy training. It is also extremely rare to find dedicated mental health teams as part of the multi-disciplinary team that make up a PKU clinic. Mental health care would havet o be carefully considered and put in place to avoid even more mental health issues with young people with PKU if the NHS are to withdraw Kuvan treatment at age 18. It also concerns me that Adult care services and children care services may already be in disagreement about levels of treatment. The submission in the Committee Papers from the Consultant in Adult Inherited Metabolic Disease states "My personal experience is also that many young people transitioning from paediatric to adult services are excessively restricting their natural protein intake and Clinical expert statement Sapropterin for treating phenylketonuria can significantly increase it without an adverse effect on their Phe levels". This doesn't bode well for "seamless" coordination between the two services and leaves young people at risk of conflicting advice. An even more frightening prospect for PKU families is when you consider that the recent COVD-19pandemic is set to cause significant additional demand for mental health care servicesin this country, especially when our mental health care service in this country is already

inadequate and underfunded. Young men's mental health is currently in the limelight butall PKU patient's mental health should seriously be considered, regardless of age.

UK Strategy of Rare Diseases
The Department of Health and Social Care recently issued a 5 Year Strategy on Rare Diseases which made promises to people with rare diseases like PKU. This documentstates:
"...we aim to ensure no one gets left behind just because they have a rare disease"
“We want to put the patients’ needs first.”
“The UK will take action... by empowering those affected by rare diseases”
“The care pathway will include.....the development of seamless pathways for transition, from childhood to adolescence, and on to adulthood and older age”
NICE need to take into consideration the promises and commitments the Government has made to people with rare diseases like PKU as currently, the Draft Guidance on Kuvan appears to pay no heed to this Strategy document and its contents.
We urge you to amend the Draft Guidance to ensure that PKU patients of all ages are offered fair and equal access to Kuvan, regardless of their age and that the dosing guidance is per the manufacturer instructions so that the dose is sufficient for adults too.

Name	
Comments on the ACD:	

Please accept this letter as my comments on your above consultation as requested.
Britain was once a leader in the field of PKU medicine. We pioneered the Guthrie test, which was adopted by the world. The NSPKU was the world’s first society for people with PKU. Our dieticians and physicians helped pioneer the use of dietary control to eliminate brain injury. We were once a leader in the world.
Sadly however Britain is now one of the worst countries in the world for the treatment of PKU. NHS services are disorganised. This leads to tragedies such as the case of a 36 yr old woman from East Anglia who was recently admitted to hospital with profound brain injury due to untreated PKU. She was found to have severe brain atrophy, was incontinent and suffering movement disorder. There are more patients in Syria funded for Sapropterin than in UK. Sapropterin is routinely funded in most countries but not in the UK. In this context it is bizarre and incomprehensible that NICE have proposed a policy which will make things even worse.
I have a number of concerns with the proposed policy which I will set out and explain below.
Involuntary removal of treatment at 18 years of age
The proposed policy requires responsive patients to have treatment up to age 18 but then for their treatment to be involuntarily withdrawn.
This treatment plan was not supported in the policy formulation stage by any clinical evidence from an appropriately qualified PKU Clinician as being feasible. As such the policy is inherently flawed as unworkable. In fact it would be profoundly damaging to the patient and is not possible.
Many responsible parents of children with PKU would consider it extremely harmful for their children to know and get used to their diet being relaxed (without the inevitable harmful symptoms of excess phenylalanine). They would be able to eat much larger quantities of proteins. This would make reverting to the PKU diet at 18 yrs a thousand times more difficult. Nowhere is this recognised or acknowledged in

the policy. It would actually be worse for their management of their PKU to be temporarily introduced to high protein levels only for it to be taken away.
Age 18 yrs is the time when the patients will be transitioning from childhood to independence. They often leave home around this time and lose the support of parents (particularly Mum) who will have had a huge input into their diet. The combination of having to take control of their own dietary management and the proposed transition is fundamentally harmful and this is nowhere recognised by the policy. This is very poor science.
Further, it is poor science to suggest the brain ceases to be vulnerable to damage at age 18 yrs. It is now recognised that brain development is not complete at age 18 and that it continues to at least age 25.
The proposed removal of treatment at age 18 is unworkable and would be harmful to patients, and is not supported by evidence.
Proposed dose
The policy proposes to limit the dose to 10mg/kg because the evidence is that this is the average treatment.
This dosage limit would be severely harmful to some patients and is unnecessary. There are many patients who require a higher dose for clinical effectiveness so for those patients the dose limit would render treatment ineffective.
The limit is unnecessary because the average dose is 10mg/kg, so this will average out over the cohort.
NICE are proposing an unjustified limit on expenditure which will cause permanent brain injury in children.
The dose limit is indirectly discriminatory as disabled children are likely to have a higher body mass due to their inability to exercise etc. NICE should allow the clinician to determine the dosage on the basis of what is in the best interests of the patient.
Women of childbearing age
The NHS policy on maternal PKU is a disgrace. NHS England made a policy for maternal PKU in 2013 which said they would collect and audit data about women, pregnancy and PKU. Yet they failed to collect any data. They also said they would review the policy – but yet they failed to review it. The policy is not working and no women are being funded for Kuvan in pregnancy. NICE have done nothing to improve this. It is a known tragedy within the PKU community that babies are being born to mothers with PKU with birth defects such as learning difficulties. This is a national scandal. It is very difficult for people to admit, and there is great shame involved.
NICE's appraisal fails to acknowledge the shocking reality of the situation. This is very poor science.
NICE state that the arrangements for women are "sub-optimal" which is a euphemism for a shambles. It is a scandal in plain sight.
Biomarin made a proposal for all women of childbearing age to be funded for Kuvan. This was rejected by NICE despite NICE accepting the position is poor. NICE's policy fails to make any attempt to deal with this unsatisfactory position which is a 3

dereliction of duty and arguably indirectly discriminatory on grounds of sex and breaches the public sector equality duty under s.149 of the Equality Act 2010.
The statement "In pregnancy, high blood Phe levels can have harmful effects on the unborn child and lead to abnormal development" (page 6, para 3.2) means that it is untenable to not make a proposal for funding to avoid fetal injury. The saving on public and other expenditure by avoiding fetal injury is immense.
Irrational statements
The NICE consultation contains statements which can only be fairly described as irrational or contradictory.

“Long-term brain damage in children is an important aspect of PKU, but there is little evidence to estimate its effect on quality of life”
One does not have to be a supposed scientific expert to work out that brain damage has quite a bad effect on quality of life. I can’t believe anyone would seriously dispute this. I think NICE should re-consider such obviously inaccurate statements and revised the policy to make common sense.
“The ERG did acknowledge that increased blood Phe levels can harm the unborn child, but the extent of lost utility is unclear, as is the effect of sapropterin on that utility loss”
I mentioned above about children of mothers with uncontrolled PKU being born with learning difficulties. The “lost utility” is an offensive term for this but any modelling of the loss would demonstrate the significant economic benefits for society of funding for Kuvan to avoid a lifetime of severe loss which results. This appears to have been discounted for reasons which have not been explained.
“There is no risk of long-term brain damage in adults”
On page 27 paragraph 3.27, NICE state there is **no** risk of long-term brain injury in adults.
This is contradictory to experience such as the 36 yr old in East Anglia mentioned above. I believe it is wrong and does not correspond with the clinical evidence. If this was correct then why does the EU guidelines recommend dietary treatment for life for all adults to keep their levels under 600 umol/l? The consensus of the scientific evidence is that adherence to those limits are strongly recommended.
White matter lesions in the brain are common in adults with PKU who are unable to adhere to diet. The lesions are damage and there is no known treatment for these lesions.
The white matter is central to cognitive processing, emotion and consciousness. NICE should adopt a precautionary approach to such damage. It should recognise that this may be very damaging. It should seek to protect the best clinical interests of patients.
Many adults in the PKU community would like to make representations to NICE about this proposal but unfortunately due to their clinical condition they lack the cognitive ability to advocate for themselves. This is somewhat grimly ironic. 4

NICE recognise that the vast majority of adults with PKU are lost to follow up by the NHS (10,000 babies a year are born with PKU but only 2,000 people with PKU in total are receiving clinical support).
NICE recognise that up to 20% of patients are unable to maintain control of their Phe levels. There are many (such as those with autism or other co-morbidity) that who are unable to adhere to dietary treatment and NICE is condemning those adults to serious permanent brain injury.
I defer to all the adults who are going to write in to you with their lived experience. Suffice it to say I much prefer their actual experience to your appraisal of the evidence which does not accord with their reality. There appears to have not been any PKU Clinicians who treat adults involved in this review. This is a major failing and may explain why the content of the policy is such poor science.
The reality for adults you need to take on board is :-
 Most adults with PKU are not on diet. Many of them were actually (wrongly) encouraged by their clinicians to give up adhering to diet.
 Even adults on diet suffer times of high levels where they suffer adverse effects
 Brain fog, lack of focus, poor cognitive functioning, headaches and memory difficulties are common
 Anxiety, depression, agoraphobia, eating disorders are common in PKU
 Other physical injuries are common including gall bladder injury, teeth injury from drinking acidic supplements, bone density problems from low calcium

The inference underlying NICE's policy seems to be that the only benefit is the ability to eat a wider range of foods. In my experience this is a very low priority of people with PKU.
Time for policy review
I note the proposal is that the guidance is reviewed only after 3 years. This is illogical as there is about to be a major relevant development – which is not even mentioned in the policy – namely that sapropterin is just about to become a generic drug. This will lead to a massive fall in the cost from the list price. It therefore makes no sense not to review the policy in the light of this change. A review in 3 months once generics are available would make more sense.
There is no justification in the policy as to why the discounted price is considered not to be cost effective. It is just a bald statement without any reasons. As such the entire policy is flawed.
Conclusion
The proposed policy is so bad is should be scrapped, and it is likely to be very harmful to the best clinical interests of patients. I would suggest that a further review should be held which should involve clinicians and patients and patient organisations.
Yours sincerely

Name	
Comments on the ACD:	

Section 1 Recommendations: Do you agree with NICE's recommendation which says that: Sapropterin (ie Kuvan) is recommended as an option for treating people with PKU only if they are under 18?

- I do not agree with stopping access to Kuvan at age 18.

Section 1 Recommendations : Do you have comments on the proposal to let children take Kuvan (sapropterin) until the age of 18 and then stop? (Your experiences about being a teenager with PKU and learning to manage dietary treatment on your own are relevant.)

It needs to be realised that 16-25 are hugely important years, maybe not in brain development as with childhood development but in so many other ways, you decide your career, decide the next step of your education, from school, to college, to university to undergrad, making new friends and worrying about your sexual health, finding a job, leaving parents, moving in with your partner or friends and figuring out who want to be as a person, what hobbies you want to get involved with and what you want to focus on I think there is a very high chance that any person growing up with PKU will go off diet around these ages, as during these times, leaving your parents or going to university tends to be peoples experimental years whether it's with relationships or drugs. Having a

whole childhood of control, it's only to be expected that PKU will be the target of experiment.

Personally, I went heavily off diet at the age of 16 for a number of reasons, that I was feeling the immense pressure that I would one day have to look after my own diet, that I was leaving school and picking my career choices yet PKU was something I would always have in my life, it would never leave me. I wanted to eat bad food but it wasn't my friends making me, the only pressure I felt from eating things I shouldn't came from myself, I wanted to enjoy food with my friends and my boyfriend, like any normal teenager would. I also went off diet at 16 because I was away from my mums control. I went to college full time and round my boyfriend's house for dinner and on the weekends, it was there I ate what I wanted whenever I wanted. Following from my earlier point, I always joke that as a teenager some people do sex, drugs and rock n' roll to rebel against their parents but I didn't do that, I did doughnuts and pizza. By the time I was 18 being off diet had affected my weight. I had gone from 9.5 stone to 12 stone. From size 8/10 to size 14, something that both affected my physical health as well as my mental health I'm still trying to lose the weight I gained to this day. All because I couldn't handle the ideal that I was becoming an adult and had to live with this diet full time. If I had been on Kuvan maybe I wouldn't have gone completely off diet but being allowed more protein a day, there would be less control in my life which causes the temptation to rebel, that feeling would have not been as strong, because it would have already been eating a kind of normal diet. I am now 27 and finally back on diet since I left at the age of 16, it took me 10 years to find the self-control, organisation, patience and self-love to get back onto the diet. If I had been on kuvan, maybe if even I would have rebelled, it would have made it a lot easier to go back to maybe 15 or 30 grams a day then the 5 grams (the same amount of protein as a slice of bread) I should have been on.

The PKU diet does not get any easier simply because we get older, there are new pressures, new responsibilities and you have to learn to do everything by yourself from a full time job, to organising your bills, to managing your weight as well as a full time metabolic condition which is only controlled by measuring and counting every bit of food you put in your mouth. And I know many people living with PKU who share the same story as I do, of going off diet because they felt so overwhelmed with the pressures off it, because they were away from their family who looked after their diet for all them all their years or because they were surrounded by temptation when you've lived with control all your life and suddenly there is no one to tell you to stop, you can't help but do whatever you want.

The decision to take away Kuvan at 18, during those fundamental years is just simply negligent, in every sense of the word. That from 0-18 someone can be on a less restrictive diet that allows them to take control of their phe levels which gives parents relief of being constantly scared of brain damage to just strip that away as soon as the PKU person has to take their first independent steps into the world and be told they now have to control their phe levels by themselves in a world full of temptations and pressures is failing to provide proper care to those with this metabolic condition, never mind the mental health effect of having a literal countdown to their 18th birthday of when they get a life changing drug taken away from them.

Section 3 - Long term brain damage in adults - NICE has said: "...adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25." NICE has also said "and there is no risk of long-term brain damage in adults". What is your opinion on NICE's statements about brain damage in adults?

- I do not agree with NICE's view
- NICE's statements are contradictory

Section 3 - Long term brain damage - Do you have experience from your own knowledge or experience about long term brain damage in adults? Is there any evidence you want NICE to take into consideration (including from your own personal or family experience?)

I was diagnosed 17 days after my birth, which when it comes to PKU is 17 days too late. As a result, I was having my mothers breast milk for those days before diagnosis which resulted in me receiving mild brain damage. My development as a child was closely observed through school, I had speech therapy from the age of 2 to 5 and had regular tests and observations through primary school to monitor how I was progressing. I was given a laptop in my first few years of secondary school due to my poor handwriting and during my GCSE exams I was able to stop and start the clock to give myself regular breaks. In college I was also given a laptop to work with. I understand that my damage affects the I have issues with mental maths, short term memory, retaining auditory information and handwriting. I was given support all through my education but once I left education at the age of 18 that is where the support stops.

You are now considered an adult and that you should be finding ways of helping yourself. In all mental illness and learning difficulties it is incredibly difficult for

adults to be diagnosed and the services to help are just simply not there in the same way that they are there for children. I am 27 and still living with the effects of long term brain damage from PKU, from both being given a late diagnosis and from going off diet between the ages of 16-25 where my levels were going between 70-1000 every month, which cannot have been good for me, Even now I am struggling with my current job, I have to take traders orders over the phone and if I don't write things down or regularly ask my customers to repeat themselves, I make small silly mistakes. I confuse part numbers (SPA1212 rather than SPA2121), quoting only 1 part and not seeing when they change their order to 2, clicking on the incorrect batch to book out from because I'm working too quickly. I get pulled up on these mistakes often by my manager who gets frustrated at me because they cost the company time and money to fix them and send out replacements. He says he wants to give me more responsibilities, but he can't until he knows I can do this basic side of my job. I enjoy my job, I have great repot with my customers, I enjoy learning all the different engineering parts we sell and enjoy the people I work with but I am scared that these mistakes are stopping me progress higher within my job and may one day result in a disciplinary or even losing my job.

I have had to find several ways around them by asking for help if I'm feeling overwhelmed, printing off physical orders rather than reading them off the screen and having coloured overlay to help me focus on the numbers. Having electronic post it note on my desktop to quickly write notes on, wearing a telephone headset so my hands can be free, triple checking all orders processed by reading every part physically out loud, having regular breaks and drinking plenty of water. It has gotten to the point where if I explain my mistakes may be the cause of my brain damage from PKU it sounds like I am just making an excuse for sloppy work.

More recently the Christmas holidays 2020, I actually emailed my adult metabolic clinic about this issue and I asked if I could be referred to a neuropsychiatrist so they may be able to provide the evidence I need, so my workplace can make the reasonable adjustments needed to help me from making these mistakes. With everything that is currently happening in the world with Covid-19 and the pressures of the NHS, unfortunately I don't know how long this referral process will take, writing this it's already been 3 months since the first initial email sent and still these issues will always live with me and affect me, they upset because it feels like it doesn't matter how hard I work, how much I bend over backwards for customers or whether I'm the only person who is always answering the phone within the first 3 rings, these mistakes always pull me back. Kuvan may be able to help children to not have issues from brain damage but what about those

adults who have already had brain damage? From either late diagnosis, poor parenting, going off diet during the developmental stages or the generation that were told by their own clinics(!) that they could relax the diet later in life. Just because there will now be children being born with PKU who will be able to go on kuvan, therefore preventing brain damage, does not mean that the adults with brain damage no longer exist, we are still here and trying to have the best quality of life possible.

Section 3 - Symptoms and quality of life. - NICE has said "Many adults describe the effects of high Phe levels as 'brain fog', forgetfulness, tiredness, confusion, low mood and feelings of irritability. This can affect their ability to control their diet and maintain adequate blood Phe levels." Do you have additional comments? What effect does high phe levels have on your quality of life?

Being Classical PKU, my tolerance to phe is incredibly low, so that means I get all of the described feelings not only when I have high phe levels but whenever my food intake fluctuates if I have not eaten enough in the day, because of how complicated cooking PKU food is, that every meal prepared for the PKU diet has to be cooked from scratch, there's no microwave meals, no ready meals, no quick fix solutions, pasta has to be cooked, sauces made from scratch, low protein pizza's constructed etc. I can come home from work tired and just not want to cook, but because I'm tired, I can't face cooking, if I can't face it I just won't eat, so I get more lethargic from not eating and too tired to cook anything, which just means I get even more easily irritable and upset. When I went off diet the brain fog, forgetfulness wouldn't just be after eating but it would follow on the next day, I've had work colleagues say they can see I'm not right the next day if we went for a meal out the night before. If I do have high phe levels, it can result in be being emotional and irritable, which affects my relationship with my husband, constantly repeating myself because I've forgotten what I've said to who.

The worst thing about the symptoms of having high phe when you're on or off diet is they are so hard to see for the person with PKU. It's not like an allergic reaction, where someone eats nuts and their throat closes up so they think "well I'm never doing that again!" Eating something for a PKU person, something as simple as wanting a pizza with some friends after a day out together will initially just result in being irritable, tired, lethargic could just be put down to not enough sleep, not drinking enough water, potential PMS etc. so you carry on not realising this is the affect it is having on you and leaves you wondering why you keep falling out with your family and friends. It takes a lot of self-discipline, reflection and mindfulness to realise the symptoms you have when you eat high protein. The worst symptom I had when I was off diet was, as well as the brain fog, tiredness and irritability was I would actually begin to slur my words, my brain

and my mouth felt unconnected so I would trip over my own words and not be able to communicate which was both upsetting and frustrating.

I am back on diet now but even if I just slip up a little bit, say I want a take away on a Friday night (as most people do!) I still feel the effects of high phe, the constant fog, frustration, irritation and upset. I would say now I'm back on diet I feel the affects even more viciously, it makes me feel so much worse which I think it has made me realise when I was off diet I must have always felt like this and never noticed because it was just normal, which must have been awful for anyone who was around me and I can't help but think but how much better I could have been in my work, friends and hobbies if I had been able to be more focused and on diet.

There are also reasons for high phe levels that are not related to going off diet necessarily, if your GP has issues getting your medication or prescription food, which was a big scare when Brexit was being planned and Covid-19 pandemic began and still is a scare for a lot of people whose GP say they can't afford the expensive food, meaning PKU's get left alone with no choice but to have high phe food. accidently eating or drinking something with unclear labels or an known ingredient change, also during illness our bodies catabolise the protein in our body to help us fight illness, but for someone with PKU this is basically the body poisoning itself, I remember during a week of flu when I was younger my blood levels went over 1000 and I was hallucinating. Menstruation in women also causes high blood levels, something that does not happen during childhood, so high phe even for someone who is strict on diet is always something that plays on a PKU's mind, the health effects are serious but the mental effects of always being scared of high levels are something that needs to be taken into consideration.

Section 3 - Long term effects of high or low phe levels on quality of life in adults : NICE say it is not necessary to take into account the long term effects of high or low phe levels in adults (ERG Report paragraph 5.3) when calculating cost effectiveness for adults. Do you agree? Do you think that having high phe levels in the past can affect your future health or life experiences? If you have information or experience to share, write it here.

I definitely think having high levels in the past affects you in the future, whether it was when you were aged 5, 15 or 35! There is no magical wipe away from having high phe levels where your brain recovers or the affects just go away. There are other issues of being off diet than just brain development. For myself, going off diet at 16-25 wasn't just affecting my brain with the symptoms of brain fog, slurred words etc. which were just as upsetting at an older age as a younger age but also I gained 3 stone over 2 years.

Which now at 27, I am still desperately trying to lose to this day, as the fat is still around my stomach which is the hardest place to lose it and may cause health

problems later in life. It's also the damage it causes to your relationships, to your career, if someone went off diet or even not as extreme, just a more relaxed diet, during university it could cause them to fail or not get the grades they could have potentially achieved.

High phe levels in the past could also cause anxiety and trauma resulting from anxiety, not having the coping mechanisms to deal with the stress of life as well as the diet and that anxiety could last for years, until dealt with cognitive behavioural therapy or actually paying for the therapist. Which again could affect relationships, friendships, finding a job.

Section 3 - Physical and mental effects of PKU and the healthcare costs associated with them. - NICE did not include healthcare costs associated with looking after patients with PKU symptoms or health problems associated with PKU. Do you think there are significant healthcare costs associated with PKU (for example treatment for depression, or gut problems?) Do you want to explain the health issues you have which are related to PKU or living with the PKU diet?

Dental problems have always been a big issue for me, as I child I was referred by the paediatric metabolic consultant to the specialists in Guys Hospital for my dental work, to prevent damage to my teeth due to the high acid contents of my amino acid drinks, the high carbohydrates and sugar content of my actual diet. At 16 I was old I had to go to a standard NHS dentist in my home town with my mother was not happy with at all, as to her even though I was over 16, so all my baby teeth had gone, all the diet issues are still there.

At 16 I also went off diet, resulting in my teeth having a complete change of diet, eating cheese, bread, even higher sugar items that I wasn't having before which resulted in having many cavities, at the time because my mum was still coming to my appointments with me, I couldn't admit to my dentist why, that I was eating foods I shouldn't have behind her back. My teeth went from perfect to having a moutful of fillings, again, something I am still struggling with now as I am due to have my second route canal and I must replace my fillings with deeper fillings as the rot has got under them, due to the sugar content of my diet. This of course has resulted in my feeling very insecure about having a mouth full of black fillings, a lot of tooth ache between appointments, time taken off work for these appointments and a lot of money spent sorting out my teeth.

The prescription costs has also been a ongoing issue for PKU's, I spend £100 a year on prescription costs to get a prepayment certificate for my substitute tablets and food. The fact we have to pay for this for the rest of our lives is ridiculous as in my eyes is no different to diabetes, they don't pay for their insulin which is just as important to their health as my substitute tablets? It's also not just the cost, I have a total 19 repeat items on my prescription, from protein free pasta, flour to snack bars and my substitute tablets. This prescription which I have to organise

like a shopping list, figuring out what I am running out of, ordering before I do, but also I (like a lot of people) have had to fight for a lot of items with my GP as they would say my biscuits are a 'luxury' item, which shows a lack of understanding of the diet as it's not like I can go into a shop and buy biscuits instead like a lot of gluten free products are available now, if I don't get if from my prescription I just can't have it.

I also had to fight to stop them removing items off my prescription if I didn't order them every month and were considered 'inactive'. It would be incredibly frustrating because like many food items you don't always fancy things some weeks and other weeks you want to eat it non stop! This may not seem important but having to fight with GP for your right to have biscuits and other food, as well as trying to maintain a low protein diet, work a full time job, manage a household and whatever else is happening in my life, prescriptions and prescription cost is just a headache that is not needed. I also know I have been one of the lucky ones, I've heard of other PKU's who weren't allowed to have their substitute from the GP because it was too expensive! Which is just awful as without the substitute you cannot function. I know many PKU's who don't have many prescription items but if you are classical PKU I think you cannot have a balanced, healthy and varied diet without prescription items. They are just a necessity for health and quality of life, a necessity that we have to pay for yearly and depend entirely on the system for, if the NHS ever does go private like the US' healthcare system, I am seriously worried that all of that could be taken away from me.

A cost that is not necessarily a high healthcare cost but a more quality of life cost is also having vegan products, which are now more regularly available in supermarkets but can make shopping for PKU's very expensive. For example, a grated bag of normal mozzarella cheese it £1.75 in Tesco, the vegan coconut grated mozzarella cheese is £2.50, feta cheese block, £1.50, vegan £2.70, 1.3L of semi-skimmed milk 80p, 1L of coconut milk is £1.50. All of these may not be necessary, but they just make a huge difference in quality of life to someone living with PKU, someone who has to basically have the same meals of prescription pasta, prescription rice, salad, potato etc. all day, it can really make a difference to actually have a pizza base with cheese that melts properly, a pasta meal with grated cheese on top, a salad with actual feta cheese. A lot of these products are also the necessary fats that PKU's lack in their diet usually so are incredibly important.

(Carer disutility) - NICE did not take into account the effect that PKU has on family members that help manage PKU symptoms or PKU treatments. What is your opinion? Do you think NICE should taken into account the impact of PKU on other family members? Do you have experience to share?

I think NICE should definitely consider family members, as they are in some way or other are basically carers to the person living with PKU, whether it's as

extreme as doing all the cooking, weighing and organising of this hugely complicated diet for their loved one or if it's just as simple as having to remind them to eat, to have their medication or to take their blood test.
High phe levels, not eating enough or not taking substitutes can result in a huge emotional full out, I'm very lucky I have a very patient and understanding husband who puts up with my eruptions of emotions and will support me through it. The mental health toll it must take on family members must be huge as well, telling your children that they can't have squash and biscuits like the rest of their friends, seeing your friend or girlfriend have an emotional breakdown when the diet gets too tough or them or their blood level comes back despite all their hard work, they have to be the strong and supportive ones for us but who can be the strong and supportive one for them?

I remember when I discovered that Dr Pepper overnight had put aspartame into their normal full fat drinks without any warning, just a different label on their bottle saying "new improve recipe!" which meant I could no longer have my favourite soft drink and to me, was just another thing that I couldn't have because of this condition I was born with, I came home and just went to bed and cried, my husband (then boyfriend) had to just hug me and say it was going to be okay to make me feel better. I can't imagine how difficult that must have been for him to see someone he loved in that much pain, all just because of a drink!

Equalities - treatment of different groups. NICE said some people may have greater difficulty managing PKU through diet. NICE have said the groups of people who may be disadvantaged include - "People who face such difficulties include: people with a learning disability, sensory impairment, or cognitive impairment• autistic people and people with comorbidities such as diabetes and gut disorders• people on low incomes, living in poor or
in insecure housing• certain ethnic groups including people who do not speak English and Gypsy, Roma and Traveller communities• people in social care settings• women with PKU who need to establish controlled phenylalanine levels before conception to avoid damage to the unborn baby." NICE concludes that it was not possible to recommend KUVAN in any group of adults "due to the cost effectiveness estimates in adults". Do you have comments about some people who have extra problems managing PKU because of their situation? Do you think NICE has properly considered treating people fairly?

My parents split up when I was 11, leaving me in a single parent household, I was incredibly lucky my mum worked in banking and then in the citizens advice bureau so could understand what help she could get, getting the benefits and tax credits needed to work part time so she could be there to support me through school with my diet and still bring in an income but I wonder how many people don't know how to find the right help when it comes to financial help, what if an adult with PKU had to go through an experience such as loosing their job, getting

a divorce, having a health crisis unrelated to PKU (cancer, heart disease etc.) a family death, an abusive relationship, just anything that would mean their world was changed forever, how could they go through that, as well as manage the extremely complex PKU diet.

I think NICE have only considered one element of life, which is brain development in children but life does not end when the brain stops developing. Adult life is far more complicated, harder, lonely, you have far more responsibility, a job where your mistakes could cost the company money or potentially lives, you no longer have the unwavering support of your parents who control every part of your life for you, you've got to figure out who you are, what you want to be, how you want to contribute to society, as well as then cooking every meal from scratch, taking substitutes drinks, tablets every day, taking monthly blood tests, organising weekly prescriptions for food, doing 6 monthly doctor appointments, how is this any less important than a developing brain?

If you then have people who are in disadvantaged situations and not giving them every help they can get, then it is neglectful, PKU is diet for life, it requires treatment for life so why are NICE not giving value to an adults life? I think NICE are really underestimating the impact Kuvan can have on a persons life, even if being on Kuvan means that would be a small change, not necessarily a complete cure but that someone could go from 5g of protein a day to 15g of protein a day, it means there would be less need to rely on prescription food, or more options to by ready meals, better lunch options and it's just one less thing to worry about in a life and world filled with so much to think about.

Women with PKU and their children - NICE has said : "The committee was not aware of any evidence to estimate the benefit to the unborn child of enhanced Phe level control or greater natural protein consumption from conception to birth and accepted that this is challenging to model." NICE has not recommended Kuvan (sapropterin) to help women manage the risk of Maternal PKU. What recommendation do you think NICE should make?

Sexual health has always been about the freedom of choice, the freedom for women to chose what they want to do with their bodies, whether to have children or not have children and currently for some women, the idea of accidently becoming pregnant with high Phe levels and so therefore accidently poisoning your own baby means that PKU takes away the choice at having children, for some as the latest studies shows, it takes away their choice to be intimate with their other halves, for fear of the potential trauma that can happen from unplanned conception.

It's just simply upsetting that the joy of creating life is taken away from us because it is such a terrifying idea that we could accidently poison our own child, that our inability to control such a restricting and diet could result in miscarriage or an abortion because the alternative is too horrible to think about. The benefits

of Kuvan for a potential mother, the chance to have potentially more protein intake and therefore the chance to have more freedom while pregnant can only have a positive impact on the unborn child as at the moment there is no choice, there is no other option then just fear.

Women with PKU and their children - NICE has said they welcome comments and further evidence on the potential use of Kuvan (sapropterin) in women with PKU of childbearing age, or those planning pregnancy, to prevent harm to the unborn child. Do you have comments or evidence to give to NICE? Things you can think about writing are....- worries about pregnancy and contraception and how this makes you feel, experiences of controlling phe levels in pregnancy, experiences after pregnancy when you have a new baby or a family, your knowledge of effects on babies/children of phenylalanine levels.

I am a 27 year old woman, married, with a career and a house of my own, so you can imagine the next natural step for me would be children but the thought of pregnancy with PKU scares me. I don't think NICE understand the impact the sentence of "Dietary measures should ideally be started before conception to avoid congenital effects."

I want to highlight the phrase BEFORE CONCEPTION, out of interest, I just put into google quickly "how long does the average couple take to conceive a child" and it comes up with the NHS website saying it can take aged 19 to 26 – 92% will conceive after 1 year and 98% after 2 years. So this is saying that conception can potentially take up to 1-2 years at least. That means if I want to have a child, I could have to be on a even more limited diet then I already am for up to 2 years **at least** and that's as long as either myself or my husband has no fertility issues, which of course are not known until you start trying for children.
1-2 YEARS of being on basically no protein, having to wholly depend on prescription food and blood levels, being constantly vigilant on diet otherwise I risk my own unborn child! As well as again, having to have a full time job, run a house hold etc. and all doing this with the stress of trying to conceive, which can add to fertility issues. This the kind of stress every women has and knows that they have to go through to have a child and that's BEFORE THE PREGANCY EVEN BEGINS.

Personally, I am still unaware of what happens during the pregnancy itself, as this isn't made clear until you decide to have a child, I don't know why but I have spoken to many women with PKU and we all have the same story to share, that we were all warned by our consultants the dangers of unplanned pregnancies, the problem is we were all told for some of us from the age of 11! I remember having that conversation and I wasn't even interested in makeup, never mind boys. But the tactic for years seems to be a fear tactic into getting women to not have unplanned pregnancies, warning of the risks and damages that can happen

to their unborn foetus. This is because there is no other option for PKU women other than just an even stricter diet and fear.

Kuvan would mean there are options, that the process of creating life can be what it should be, a fun beautiful miracle of life and an expression of love, not just a constant state of fear. I think this is fear is always in the back of women's minds, whenever they see a child, whenever they hear a colleague at work declare that they're going to be having a baby and it's a big surprise. That happened to me the other month at work and walked home from work crying, wondering whether I would be able to get that moment for myself, as our family members will have to know we are trying for a baby so they can cater for me for my more extreme pre-con (pre-conception) diet, if I've been on the conception diet everyone will know why, we won't get the 3 months of privacy that are needed in case something goes wrong, everyone will know and everyone will know if something isn't working.

Women with PKU and their children : NICE has not included the costs of preventing neurological damage to the children of women with uncontrolled PKU (ERG report, section 5.5) in their costs calculations. Do you have any comment?

As I have said before, the only tactic currently with PKU women and pregnancy is just fear, it's panic and it's an extremely controlled strict diet, I have been trying to get back on diet strictly for the past year so if we one day do decide to have children the jump down to the pre-con diet isn't so hard, but for those off diet, for whatever reason, whether their can't manage their diet due to work, they find the diet too restrictive and stressful, they were told as a young person they could go off diet as an adult etc. to then be told they suddenly have to barely eat anything, and it really is as extreme as that must be hugely stressful and not something they may be able to cope with, they may be tempted during pregnancy to eat normally because they've not learnt the tactics or cooking skills to be able to cater for the PKU diet, which would cause damage in the baby. Kuvan would mean that this jump is not so hard, that there are choices and that there is no need for temptation or stress.

Do you have any additional comments on the draft recommendation or the evidence NICE has considered?

I don't think NICE have considered the impact Kuvan can truly make on an adult's life at all, they've just seen there's a higher cost and that it's too much for them to justify, that our brains may have technically finished developing but they forget that people are so much more than just brains.

Whether people are great responders of Kuvan or they barely respond, PKU is such a hard, lifelong, daily condition, there are no two days alike, and no two PKU people alike, the people who are managing fine on diet and the people who

are struggling or are off diet still need the same amount help, both are still valid to who should be allowed this potentially life changing treatment just as much as both children and adults deserve it. Life does not get easier because you've suddenly turned 18, you are now potentially by yourself, organising a diet that your parents had managed for you your whole life, that your parents had 18 years worth of experience on how to cook, to talk to people about it, to manage the symptoms and off days. You now have to balance full time education, a full-time job, relationships, friendships, managing a household, managing your own exercise and mental health and having to make every meal, count every gram of protein, resist temptation of fast eating, fast food and the social pressure that comes with eating a meal.

I am on 5 grams of protein, my day consists of having 60g of vegan yoghurt, 6g of rice krispies with fruit for breakfast, that's 1g of protein. At work for lunch and snacks I have carrot sticks which are free, fruit which is free, a packet of crisps which are 1g of protein, a vegan moose which is 1g of protein, prescription pasta meal with veg, tomato sauce and vegan Greek cheese, that meal is free and I would have cooked first thing in the morning, prescription biscuits for my afternoon snack and I've spent the day having a black coffee in the morning and herbal tea throughout the day as I can't have milk for tea. So far, I have had 3g of protein. I then come home and cook myself some boiled potatoes for the 2g of protein I have left, this would be 180g of potato I have a salad with this and maybe a vegan jelly for pudding. That is on a good day when I get up in time in the morning to cook pasta, when I've remembered to buy potatoes or salad needed for something on the side. Other days I don't have breakfast, I just have soup and toast for lunch and for dinner I have oven chips with nothing else on the side.

I can't help but think back to the boy who won the chase to be able to be on treatment and go from 5g like me, to 15g a day. I may not be eating cheese and pickle sandwiches any time soon (20g of protein) but it would mean portion sizes are more generous, I could have a bowl full of rice krispies, rather than just 6g of rice krispies. I could have a warm bowl of porridge for breakfast! That I wouldn't have to weigh how many potatoes I can have, I can take more filling snacks to work, I wouldn't have to rely on prescription food and the 3-4 day wait it takes to hand in a prescription, for the to tick them off and the pharmacy to source the items to then call and tell me I can pick them up and as I don't have a car I have to carry a box full of food back home.

I don't think NICE have also considered the amount of discipline, stress, mental health affects for trying to get back onto the diet as well, I was off diet from the

age of 16-25 and it was incredibly hard to try to get back into the mind of weighing every single item of food you eat, from going from eating everything to seeing how much 1g of protein is in rice krispies (13g), barely a third of a bowl. Trying to have substitutes that are either a horrible favour, incredibly awkward to make out and about or you have to take thousands of tablets a day (I am currently on microtabs and I have to take around 1360 tablets a day currently). To tell friends and family who have always known you don't eat meat but usually you eat everything else that they need to change how they cook for you, which they may either take personally or think you are being hypocritical. Trying to do regular blood tests, the only way you can actually see if what you are doing is making any changes to your blood levels, only to be told by your doctor you can only do 1 a month, for the blood test to get lost in the post, or that the blood was contaminated because the cat accidently walked over it. To have to learn to cook from scratch, to try and see what vegetables you like and end up buying too many so you have to waste a lot of food before you realise what you like. The battling with the GP to get more food on your prescription so you can have more 'free' food in your life, trying different food diaries, different substitutes, different meal plans and then when you do finally get into a good routine of weighing, counting, cooking, taking all your substitutes every day, planning your prescriptions you then realise you have to do this constantly, every day, for the rest of your life. There is no respite, no days off, no 'cheeky' snacks or take aways, this is now your life.

I don't think NICE or anyone who doesn't live with PKU every day truly understands the mental impact living with PKU has on an adult every single day and again, this is all while you are trying to have a full time job, manage a household, take care of friends and family, go on holiday, exercise, have a hobby and everything else that comes with life. For everyone without PKU, food is just something to enjoy, to binge on, to feel guilty for having one more slice of cake and gives them energy, for someone living with PKU, it is a constant presence of control, brain damage, pain and the awareness that you will forever be different. For me personally, the only reason I ever got back on diet was due to the 2020 lockdown in the spring. It gave me that time away from work, to actually focus on my diet, to focus on the food I was eating, creating a food diary that worked for me and to finally get a sense of routine. Without that lockdown I would not be where I am today with my diet, and all that I needed was a global pandemic! What if I never had that time? What if I was still working non stop for years, on a knives point of barely being only diet but as soon as something would go wrong I could fall back down again? It should say everything about how difficult this diet

is that it literally took the world coming to a stop for me to find the space and time to control it.

It's not just the food either, with Kuvan it would mean my Phe levels would be under better control, I could think clearer, be more emotionally available to my friends, to able to focus better at work, feel less lethargic and hungry all the time, not have the stress of what my next blood level would be. I would actually be able to enjoy food, enjoy socially eating with friends without worrying about being awkward or sticking our people having to make special allowances for me.

This is the impact Kuvan would make on just one adult, and I have no doubt that this is the impact Kuvan would have on every adult. To brush us away as "well we've developed so therefore we aren't cost effective" is just so painful to hear as we don't stop learning as soon as we turn 18 either, we have to learn new skills for jobs or hobbies, develop new habits for exercise, new social graces for jobs, meetings, family. Your brain is making new memories, new connections every day and if high phe or unmanaged diet has even a slight chance of damaging that, we need every single option possible available to us so we can live as full as life as possible.

I have attached on the next page my blood levels for the last 10 years, provided to me by my metabolic consultant for the purposes of this response. The EU recommended guidelines are that blood levels should be under 600umol/L, (where I have put the red line) as you will be able to see, my blood levels since the age of 16 have barely been under that line, the reasons why given my previous answers. I have labelled the different ages, at the age of 25 you will notice I had a sudden very low level, that was because for those months I had paid for a personal trainer to do a diet and fitness plan for me. You will see the moment when lockdown begun and with nothing to do but focus on food and diet, I was finally able to get my blood levels under that line through most of 2020. Global lockdowns and paying for a personal trainer out of your own pocket is not something that a person should have to do when being born with a genetic condition, something that is not their fault and they have to live with for the rest of their lives, this is support and a service that should be provided by our national health service, yes it is an expensive cost and maybe on paper isn't 'cost effective' but the difference in quality of life for some with PKU of being on diet, being at the best possible mental ability, being in control of their lives and having freedom to eat food! Like a normal person is not something that should be dismissed so easily, as NICE's decision to stop Kuvan at 18 has exactly done, we are still humans, we are still valid and we still deserve the best possible treatment so we can live our best life.

Name	
Comments on the ACD:	

Dear TA Team 1,
We are writing to comment on your recommendations We are parents with the benefit of over 38 years' experience of bringing up a child with PKU and supporting her through school, university, work and life as an adult.

We welcome the proposal to recommend the use by the NHS of Kuvan for children but believe that patients of all ages with PKU who respond to the drug should be able to use this medicine as part of their care by the NHS.

Stopping treatment at age 18

We believe NICE has not properly considered the problem of young people stopping treatment with Kuvan at 18 and then embarking on a diet without it. Managing phenylalanine levels with diet alone is very difficult and 18 year olds used to a relaxed diet with Kuvan will find it difficult to switch to the constant preparation of meals, precise measurement of food, regular self – administered blood tests, management of prescriptions (many GPs are unaware of the PKU diet and can be reluctant to prescribe special dietary foods), the difficulties in participating in social activities including eating out. At 18 many are leaving home to go to university and starting work. That is not the time to have a major change in diet which may lead to poorer concentration, low mood, anxiety etc as attested in the evidence given to you.
We also believe that a PKU sufferer not brought up with the various supplements needed in greater quantities after 18 would find them very hard to stomach as they are extremely unpalatable. This change after 18 would result in many going off diet and having much poorer health. This would adversely affect their life chances of getting the careers, work and educational opportunities they need to live.
We well remember the difficulties faced when our daughter went away to university and despite having prepared well by learning to cook and manage the diet, she experienced a great deal of anxiety and stress on trying to cope with the diet, follow her course of studies and adapt to university life.
We note the contradiction in the statements from NICE that brain development continues after 18 until age 25. Indeed current scientific research suggests the brain is constantly changing and developing throughout life. NICE seems to suggest potential brain damage after 18 is acceptable.

Maternal PKU Syndrome

NICE does not seem to have understood the situation of adult PKU women and pregnancy. This subject causes a great deal of anxiety to women and their families which often leads to reluctance to have children, with the consequent loss of the normal human pleasure of seeing one's family grow with children and grandchildren. When deciding that Kuvan is not cost effective in adults, NICE has ignored the benefits to women with PKU of using Kuvan to help them have happy intimate relationships without having to worry about an unplanned pregnancy resulting in Maternal PKU syndrome, and have safe and happy pregnancies, whether planned or not.

NICE has recognised that controlling Phe levels is important in early pregnancy, ideally before conception, and has recognised that this would reduce the risks of Maternal PKU Syndrome. However, the harms to mother and child through high Phe levels in early pregnancy have not been included in the cost analysis.

The mental & physical experiences of women with PKU who have gone through the pre-conception diet and a pregnancy (a time when hormonal and other health changes are significant) have not been taken into account. Pregnancy can also result in severe illness that makes the diet even more difficult, both mentally and physically. All these difficulties and more are articulated by PKU patients in

Ford, O'Driscoll & MacDonald "Reproductive Experience of Women living with PKU", Molecular Genetics& Metabolism Reports 17 (2018) pp. 64-68.

As more early treated adults go into middle age and the menopause hits women, Kuvan could help with dietary compliance at a time when hormonal changes make life very difficult. Women PKUs are at more risk of osteoporosis and a more relaxed diet with more natural protein would be of benefit.

All this should be taken into account. Unfortunately the tone of the NICE recommendations is, to us, very dismissive of the needs of women with PKU.

Living with PKU

In failing to recommend use of Kuvan for over 18s we believe that NICE has undervalued the work and impact that managing PKU has on the adult PKU and their families. A great deal of time is spent by PKUs in looking after themselves and controlling their diet so as to avoid suffering the symptoms of high Phe levels. Studies such as

Ford, O'Driscoll& MacDonald "Living with Phenylketonuria: lessons from the PKU Community" Molecular Genetics &Metabolism Reports 17 (2018) pp.57-63 give detailed accounts of the lived experiences of PKUs. The draft recommendations do not take into account the positive economic, health and social impacts of more people working and achieving more in their careers, contributing to their communities and being more active members of society, all of which would be possible with better Phe levels through use of Kuvan and any other new treatments that are created to treat PKU.

NICE has ignored that many adults with PKU who have problems associated with high Phe levels (brain fog, depression, poor memory) simply cannot cope with dietary treatment. The NHS should not leave these people without a realistic option for treatment. Many adults who experience problems were told by the NHS when they were children in the 1970s – 1990s that they did not need to continue the diet in their late teenage years and in adulthood and so didn't, trusting the advice. NICE is not taking into account that they were advised in this way, and that Kuvan could be a very significant help to them.

Adult PKUs with learning disabilities are at higher risk of being unable to control their Phe levels with diet and whilst NICE recognised this problem there is no apparent evidence in the consultation that this has been included in the cost analysis.

Treatment with Kuvan

We note the recommendation in the document of a specific dose for treatment of under 18s. however we believe clinicians should be able to treat suitable PKUs within the range advised by the manufacturers.

Conclusion

After so many years of waiting it is a bitter blow for NICE to deny the possibility of this treatment to adult PKUs. We are very disappointed that NICE has failed to attempt to bring into the cost analysis a factor to reflect the benefits to the NHS and our society, of PKUs who respond to the treatment being able to live happier, healthier lives.

We believe the NHS should give all PKUs the opportunity to try Kuvan and if they respond, to have the treatment by the NHS.

We know only a proportion of PKUs respond to Kuvan and the cost to the NHS will be insignificant compared to the vast sums spent on preventable diseases such as type 2 diabetes.

Perhaps it is the case that NICE regards PKU sufferers as a minority that can be disregarded, without attempting to fully understand the very onerous burden they carry for life and using a cost benefit analysis which takes account of all factors, not just financial ones.

Name	Rt Hon Sir Mike Penning MP
Comments of the ACD	

To Sapropterin Consultation

I am very concerned at the draft guidance proposed for the prescription of Sapropterin (Kuvan) for patients with Phenylketonuria (PKU).

Specifically, I am concerned that the drug be prescribed only up to the age of 18 and that from the age of 18, patients are deemed to be adults and expected to manage the situation with aid of a dietary regime instead.

For a young person leaving home and going to university, college or first-time employment, this is a difficult and totally unrealistic expectation on top of all the other changes going on in their lives at that time. Such a dramatic change and intensely restrictive regime will clearly have a tremendous adverse impact on their mental health – at a time when all their contemporaries are enjoying new-found freedoms and life experiences. When most teenagers celebrate their 18th birthday, PKU patients will be dreading it. 18 seems to be such a cruel cut off point.
The supporting document states:

“However, adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25.”

So, it seems to me that if young people are still at risk until the brain stops developing at around 25 years of age, then we should surely be offering sapropterin until that age at very least. I believe we really need to be offering sapropterin until such a time as is appropriate depending on the individual circumstances of the patient. Surely, we should let the individual decide when is an appropriate time to move over to a dietary regime solution?

I am further concerned, that the guidance proposed to restrict the dose to 10 mg. This is not in accordance with the manufacturer's guidance. The manufacturer's recommended dose is based on weight, so clearly many teenagers will not receive a sufficient quantity of the drug for it to be effective. This could result in them being defined as 'non-responsive', and thus having the drug discontinued in error. My view is that clinicians should have the flexibility to adjust the dose within the effective dose range recommended by the manufacturers of up to 20mg.

I have been contacted by constituents whose son, who is in his early 20s, has PKU and has found it impossible to adhere to the incredibly restrictive dietary therapy. He is devastated that he will not be eligible to receive KUVAN which would be life-changing for him. He has been promised, since the age of 8 under the care of Great Ormond Street Hospital, that this drug would one day be available to him. He is now giving up hope of ever receiving a drug to treat his disease, despite the fact that had he lived in one of over 50 countries worldwide, including Croatia, Turkey, Russia and the Middle East he would have been able to access it.

Quite simply, it seems that we keep repeating the same mistakes we have made before. We have a wonderful NHS in the UK, but so often it fails the smaller groups who need specialist support – where these groups would get support if they lived in other countries. It took a long fight to get Orkambi and associated drugs approved for cystic fibrosis, it would be very disappointing if we have to go through all that with PKU.

I urge you, therefore, to amend the draft guidance before it is too late so that sapropterin is available to people with PKU of all ages and the dosage range to be that as recommended by the manufacturer.

Name	
Comments on the ACD:	

I write in regards to the recent Kuvan decision and wish to put my comments forward.

The logic behind only offering Kuvan to the age of 18 is extremely worrying. Children and teens will get used to a more relaxed diet and then be expected to return to a full diet at the age 18. This will be unfamiliar to them and cause massive mental health and physical health implications.

The discrimination of the drug only being offered to children is wrong. PKU doesn't stop at 18! The drug would make a huge difference to the lives of adults. There is a lot of information and evidence of adults struggling in later life with anxiety, depression, phobias, poor memory. This is extremely worrying for my own child when they move into adulthood and need to cope at University or in the workplace. The drug would support them but if taken away at 18 , the effects would be detrimental.

If all adults were on Kuvan it would also help in pregnancies. If ladies are already on the drug then this would help with unplanned pregnancies. I know the impacts of caring for a special needs child and it's a huge life changing situation. This could be avoided for many people if they are already on the drug.

The dosage doesn't make sense at all. Why offer a drug but not have the full workings of it. Would a diabetic patient only be offered half their insulin. For a drug to work efficiently and effectively the full amount needs to be administered. The unfairness of this is not justified.

I feel there has been a lack of true understanding of pku and the benefits of kuvan for children and adults. This drug works wonders for patients who respond to it and it is proven to be clinically effective. All pku patients should have the right to this drug. They haven't chosen to have pku. It is a condition from birth straight through to adulthood. Patients should be helped in every possible way to improve their quality of life.

Yours faithfully,

Name	
Comments on the ACD:	
I am pleased that NICE has recently recommended that children with PKU should be allowed to use the treatment Kuvan up to the age of 18. That is very welcome news. I am puzzled, however, about the proposal to stop prescribing it at that age, since medical authorities recommend that the strict PKU diet should be followed for life. My grandson with PKU is now 25 and has to be constantly vigilant with his restricted diet. I know that many adults with PKU have serious problems caused by high phenylalanine levels such as reduced concentration, lack of energy and poor memory. We are ever-alert to these problems. When one explains to people that PKU is a disorder which is treated by diet, it sounds an easy process, as though it could be something like a voluntary weight-loss diet or a life-style choice. It is not like that at all: restricting the amount of protein in everyday life involves an exhausting 24- hour- a- day, 7- day- a- week attention, year after year, and has a very great effect on family and social life. Access to Kuvan would be a tremendous help to both children and adults alike. I do hope that NICE will be able to extend their recommendation for this treatment for PKU patients above the age of 18.	

Name	
Comments on the ACD:	
Dear TA Team 1, I am writing in response to your consultation as a friend of an adult with PKU. I welcome the recommendation that children can use Kuvan. In addition, in line with National Society for PKU (NSPKU)'s views on the draft guidance, I believe that patients of all ages with PKU who respond to treatment with Kuvan should be able to use this medicine. NICE has not considered the problem of young people stopping treatment with Kuvan on their 18th birthday. Managing phenylalanine levels with dietary treatment	

alone is very difficult, especially for teenagers leaving home, starting work, and establishing themselves as adults in the world. Brain development continues until age 25, and 18 year-olds accustomed to a very relaxed diet through using KUVAN will not have the coping skills to switch to a strict diet which involves constant preparation of meals, precise measurement of all foods, constant management of prescriptions, regular self-administered blood tests, and difficulties in participating in social occasions based around food, including eating out in restaurants. It will lead to people not continuing the diet, being lost to treatment and having health issues related to high phenylalanine levels in adulthood. NICE has ignored this issue completely.

NICE's analysis underestimates the benefits of KUVAN treatment for adults with PKU. NICE says there is no risk of permanent damage to the brain after the age of 18, but this is contradicted by other statements made by NICE in the document which recognise that permanent harm can occur after the age of 18 and that brain development continues until age 25. There is good evidence that many adults with PKU have very serious symptoms caused by high phenylalanine levels in adulthood. These problems in adults are undervalued by NICE. Furthermore, new research into neuroplasticity and more recently neurogenesis is showing more clearly that the brain continues to change and develop throughout life. NICE has ignored that the adult brain does not stop changing and developing.

NICE has not considered the harm of Maternal PKU Syndrome and the worry this can cause to women with PKU throughout their lives until the menopause. When deciding that Kuvan is not cost effective in adults, NICE has ignored the benefits to women with PKU of using Kuvan to help them have happy intimate relationships without having to worry about an unplanned pregnancy resulting in Maternal PKU Syndrome, and have safe and happy pregnancies, whether planned or not. NICE has recognised that controlling phe levels is important in early pregnancy, ideally before conception, and has recognised that this would reduce the risks of Maternal PKU Syndrome. However, the harms to mother and child from high levels in early pregnancy have not been included in the cost analysis. The mental and physical experiences of women with PKU who have gone through the pre-conception diet and a pregnancy, a time when hormonal changes and other health changes due to pregnancy are significant, have not been taken into account. Pregnancy can also result in severe illness that makes the diet even more difficult both mentally and physically. All of these difficulties and more are articulated by PKU patients in Ford, O'Driscoll, and MacDonald, 'Reproductive Experience of Women Living with PKU', Molecular Genetics and Metabolism Reports 17 (2018), pp.64-68, which NICE needs to take into account. The hormonal changes experienced by women during the menopause should also be taken into account as more early treated adults go into middle age: women need help to ensure they can maintain low phenylalanine levels throughout life. I believe that NICE has failed to take account of the issues experienced by women with PKU and that this is a major failing in the draft guidance.

NICE has ignored that many adults with PKU who have problems associated with high phenylalanine levels – like brain fog, depression, or poor memory – simply cannot cope with dietary treatment. The NHS should not leave people without a realistic option for treatment. Also, many adults who experience difficulties were told by the NHS when they were children in the 1970s-1990s that they did not need to continue the diet in their late teenage years and in adulthood, and so didn't, trusting their clinicians. The NICE draft guidance does not take into account that they were advised in this way, and that Kuvan would help them control their phenylalanine levels. It is also not clear that NICE has considered the improved economic contribution that adults with PKU could make to if they were not suffering from the problems like brain fog, depression and poor memory which are associated with high phenylalanine levels.

I also believe that NICE has undervalued the work and impact that managing PKU can have on adults with PKU and their families. People with PKU spend a lot of time looking after themselves and controlling their diet, or suffering the symptoms of high phenylalanine levels. This is clear from studies such as Ford, O'Driscoll, and MacDonald, 'Living with Phenylketonuria: Lessons from the PKU Community', Molecular Genetics and Metabolism Reports 17 (2018) pp.57-63 which gives a detailed account of the lived experiences of people with PKU. Also, the draft guidance does not take into account the positive economic, health, and social impacts of having more people working and achieving more in their careers, contributing to their communities, and being more active members of society, all of which would be possible with their phenylalanine levels better controlled through the use of Kuvan and any other new treatments that are created to treat PKU. People with learning disabilities are at a higher risk of being unable to control their phenylalanine levels with dietary treatment. The need for help with dietary treatment might also restrict the independence of people with learning difficulties. NICE recognised that people with learning difficulties might struggle with dietary treatment but there is no evidence that this has been included in the cost analysis in this consultation document.
NICE has recommended using KUVAN at a dose of 10mg/kg. I agree that clinicians in the UK will prescribe more efficiently than in the US and that an average dose of 10mg/kg is appropriate for the cost analysis. However, I believe that clinicians should be able to prescribe within the marketing authorisation, which ranges from 5mg/kg to 20mg/kg.
I believe that all people with PKU should have access to Kuvan on the NHS, and all future treatments for PKU that become available should also be funded to enable people with PKU to live freer, happier lives, and fulfil their potential.

Name	
Comments on the ACD:	
As the grandfather of a three-year-old girl I welcome the progress that is being made in the treatment of everyone with the metabolic disorder PKU however feel strongly that Kuvan (Sapropterin) should be available to patients of all ages who respond to treatment. NICE appears to have completely ignored the physical and psychological problems of teenagers, already experiencing the change from childhood to adulthood, having to cope with an unexpected and thoroughly unwelcome 18th birthday present; suddenly stopping their treatment with Kuvan. Managing Phenylalanine based on dietary treatment alone is very difficult, more so with teenagers. It is easily foreseeable that those who have become accustomed to a more relaxed diet through using Kuvan will lack the skills to switch to more restricted diets. Additionally many will probably be away from home for the first time; for example, at university, in new jobs or possibly serving in the armed forces thus increasing the problem of remaining fit and healthy in their new life. NICE has undoubtedly underestimated the benefits of KUVAN for adults. On the one hand it acknowledges that high levels of phenylalanine in adulthood can cause brain damage yet elsewhere contradicts this assertion. It seems oblivious to the fact that many adults with PKU suffering high levels of phenylalanine which cause	

brain fog, depression or, memory lapses cannot deal with dietary treatment. Patients should not be left without a realistic option for treatment.

As a layman and from my reading of the draft consultation it is alarming that NICE has underestimated the effect that managing PKU can have on individuals and their families. Even more worrying is the fact that NICE has failed to consider the harm of Maternal PKU syndrome. Effectively it is denying women with PKU the opportunity to have safe and happy pregnancies by refusing them KUVAN. One would also have thought that reducing the harm in early pregnancy caused by high levels of phenylalanine would have been included in any cost analysis.

It is a given that those with PKU who are additionally affected with learning disabilities should be included. Again there appears to be little evidence that this has been adequately analysed with regard to cost.

From my standpoint there seems to be an arbitrary decision to restrict KUVAN to 10mg/kg doses. Surely experienced clinicians should be left to prescribe what they consider necessary or the individual i.e. 5mg/kg, 10mg/kg and 20mg/kg which, I understand is within the marketing authorisation.

I also find it astonishing that the UK as a whole continues to drag its heels over this issue, presumably largely because of cost, when cheaper generic versions of Sapropterin will be available shortly. It is astonishing that elsewhere in Europe those with this particular metabolic disorder are prescribed Kuvan but denied the treatment in the England and Wales.

I trust that NICE will consider and take on board many of the comments and suggestions have received from anyone who has knowledge of this condition and there will be a satisfactory outcome for all concerned.

Name	
Comments on the ACD:	
Dear TA Team 1, I welcome the recommendation that children can use Kuvan but I believe that patients of all ages with PKU who respond to treatment with Kuvan should be able to use this medicine. I write this as a friend of an adult with PKU, which means I've seen the impact PKU has on the life and well-being of those affected by it. I've been lucky that my friend has confided in me of their struggles and it is due to this that I strongly believe that people of all ages with PKU should be able to access this potentially life-changing medicine. NICE has not considered the problem of young people stopping treatment with Kuvan on their 18th birthday. Managing phenylalanine levels with dietary treatment alone is very difficult, especially for teenagers leaving home, starting work, and establishing themselves as adults in the world. 18 year-olds accustomed to a very relaxed diet through using KUVAN will not have the coping skills to switch to a strict diet which involves constant preparation of meals, precise measurement of all foods, constant management of prescriptions, regular self-administered blood tests, and difficulties in participating in social occasions based around food, including eating out in restaurants. It will lead to people not continuing the diet,	

being lost to treatment and having health issues related to high phenylalanine levels in adulthood. NICE has ignored this issue completely.
NICE's analysis underestimates the benefits of KUVAN treatment for adults with PKU. NICE says there is no risk of permanent damage to the brain after the age of 18, but this is contradicted by other statements made by NICE in the document which recognise that permanent harm can occur after the age of 18 and that brain development continues until age 25. There is good evidence that many adults with PKU have very serious symptoms caused by high phenylalanine levels in adulthood. These problems in adults are undervalued by NICE. Furthermore, new research into neuroplasticity and more recently neurogenesis is showing more clearly that the brain continues to change and develop throughout life. NICE has ignored that the adult brain does not stop changing and developing.
NICE has not considered the harm of Maternal PKU Syndrome and the worry this can cause to women with PKU throughout their lives until the menopause. When deciding that Kuvan is not cost effective in adults, NICE has ignored the benefits to women with PKU of using Kuvan to help them have happy intimate relationships without having to worry about an unplanned pregnancy resulting in Maternal PKU Syndrome, and have safe and happy pregnancies, whether planned or not. NICE has recognised that controlling phe levels is important in early pregnancy, ideally before conception, and has recognised that this would reduce the risks of Maternal PKU Syndrome. However, the harms to mother and child from high levels in early pregnancy have not been included in the cost analysis. The mental and physical experiences of women with PKU who have gone through the pre-conception diet and a pregnancy, a time when hormonal changes and other health changes due to pregnancy are significant, have not been taken into account. Pregnancy can also result in severe illness that makes the diet even more difficult both mentally and physically. All of these difficulties and more are articulated by PKU patients in Ford, O'Driscoll, and MacDonald, 'Reproductive Experience of Women Living with PKU', Molecular Genetics and Metabolism Reports 17 (2018), pp.64-68, which NICE needs to take into account. The hormonal changes experienced by women during the menopause should also be taken into account as more early treated adults go into middle age: women need help to ensure they can maintain low phenylalanine levels throughout life. I believe that NICE has failed to take account of the issues experienced by women with PKU and that this is a major failing in the draft guidance.
NICE has ignored that many adults with PKU who have problems associated with high phenylalanine levels – like brain fog, depression, or poor memory – simply cannot cope with dietary treatment. The NHS should not leave people without a realistic option for treatment. Also, many adults who experience difficulties were told by the NHS when they were children in the 1970s-1990s that they did not need to continue the diet in their late teenage years and in adulthood, and so didn't, trusting their clinicians. The NICE draft guidance does not take into account that they were advised in this way, and that Kuvan would help them control their phenylalanine levels.
I also believe that NICE has undervalued the work and impact that managing PKU can have on adults with PKU and their families. People with PKU spend a lot of time looking after themselves and controlling their diet, or suffering the symptoms of high phenylalanine levels. This is clear from studies such as Ford, O'Driscoll, and MacDonald, 'Living with Phenylketonuria: Lessons from the PKU Community', Molecular Genetics and Metabolism Reports 17 (2018) pp.57-63 which gives a detailed account of the lived experiences of people with PKU. Also, the draft guidance does not take into account the positive economic, health, and social impacts of having more people working and achieving more in their careers, contributing to their communities, and being more active members of society, all of

which would be possible with their phenylalanine levels better controlled through the use of Kuvan and any other new treatments that are created to treat PKU.
People with learning disabilities are at a higher risk of being unable to control their phenylalanine levels with dietary treatment. The need for help with dietary treatment might also restrict the independence of people with learning difficulties. NICE recognised that people with learning difficulties might struggle with dietary treatment but there is no evidence that this has been included in the cost analysis in this consultation document.
NICE has recommended using KUVAN at a dose of 10mg/kg. I agree that clinicians in the UK will prescribe more efficiently than in the US and that an average dose of 10mg/kg is appropriate for the cost analysis. However, I believe that clinicians should be able to prescribe within the marketing authorisation, which ranges from 5mg/kg to 20mg/kg.
I believe that all people with PKU should have access to Kuvan on the NHS, and all future treatments for PKU that become available should also be funded to enable people with PKU to live freer, happier lives, and fulfil their potential.

Name	
Comments on the ACD:	

Dear TA Team 1,
I welcome the recommendation that children can use Kuvan but I believe that patients of all ages with PKU who respond to treatment with Kuvan should be able to use this medicine. I write this as the cousin of an adult with PKU. Her life has been extremely challenging from ever since I can remember and I really feel frustrated with the approach being considered here. As a nearly 40yr old adult she is impacted by this condition and placing this type of approach for an 18 yr old or anyone is saddening.
NICE has not considered the problem of young people stopping treatment with Kuvan on their 18th birthday. Managing phenylalanine levels with dietary treatment alone is very difficult, especially for teenagers leaving home, starting work, and establishing themselves as adults in the world. 18 year-olds accustomed to a very relaxed diet through using KUVAN will not have the coping skills to switch to a strict diet which involves constant preparation of meals, precise measurement of all foods, constant management of prescriptions, regular self-administered blood tests, and difficulties in participating in social occasions based around food, including eating out in restaurants. It will lead to people not continuing the diet, being lost to treatment and having health issues related to high phenylalanine levels in adulthood. NICE has ignored this issue completely.
NICE's analysis underestimates the benefits of KUVAN treatment for adults with PKU. NICE says there is no risk of permanent damage to the brain after the age of 18, but this is contradicted by other statements made by NICE in the document which recognise that permanent harm can occur after the age of 18 and that brain development continues until age 25. There is good evidence that many adults with PKU have very serious symptoms caused by high phenylalanine levels in adulthood. These problems in adults are undervalued by NICE. Furthermore, new research into neuroplasticity and more recently neurogenesis is showing more clearly that the brain continues to change and develop throughout life. NICE has ignored that the adult brain does not stop changing and developing.
NICE has not considered the harm of Maternal PKU Syndrome and the worry this can cause to women with PKU throughout their lives until the menopause. When deciding that Kuvan is not cost effective in adults, NICE has ignored the benefits to women with PKU of using Kuvan to help them have happy intimate relationships

without having to worry about an unplanned pregnancy resulting in Maternal PKU Syndrome, and have safe and happy pregnancies, whether planned or not. NICE has recognised that controlling phe levels is important in early pregnancy, ideally before conception, and has recognised that this would reduce the risks of Maternal PKU Syndrome. However, the harms to mother and child from high levels in early pregnancy have not been included in the cost analysis. The mental and physical experiences of women with PKU who have gone through the pre-conception diet and a pregnancy, a time when hormonal changes and other health changes due to pregnancy are significant, have not been taken into account. Pregnancy can also result in severe illness that makes the diet even more difficult both mentally and physically. All of these difficulties and more are articulated by PKU patients in Ford, O'Driscoll, and MacDonald, 'Reproductive Experience of Women Living with PKU', Molecular Genetics and Metabolism Reports 17 (2018), pp.64-68, which NICE needs to take into account. The hormonal changes experienced by women during the menopause should also be taken into account as more early treated adults go into middle age: women need help to ensure they can maintain low phenylalanine levels throughout life. I believe that NICE has failed to take account of the issues experienced by women with PKU and that this is a major failing in the draft guidance.

NICE has ignored that many adults with PKU who have problems associated with high phenylalanine levels – like brain fog, depression, or poor memory – simply cannot cope with dietary treatment. The NHS should not leave people without a realistic option for treatment. Also, many adults who experience difficulties were told by the NHS when they were children in the 1970s-1990s that they did not need to continue the diet in their late teenage years and in adulthood, and so didn't, trusting their clinicians. The NICE draft guidance does not take into account that they were advised in this way, and that Kuvan would help them control their phenylalanine levels.

I also believe that NICE has undervalued the work and impact that managing PKU can have on adults with PKU and their families. People with PKU spend a lot of time looking after themselves and controlling their diet, or suffering the symptoms of high phenylalanine levels. This is clear from studies such as Ford, O'Driscoll, and MacDonald, 'Living with Phenylketonuria: Lessons from the PKU Community', Molecular Genetics and Metabolism Reports 17 (2018) pp.57-63 which gives a detailed account of the lived experiences of people with PKU. Also, the draft guidance does not take into account the positive economic, health, and social impacts of having more people working and achieving more in their careers, contributing to their communities, and being more active members of society, all of which would be possible with their phenylalanine levels better controlled through the use of Kuvan and any other new treatments that are created to treat PKU.

People with learning disabilities are at a higher risk of being unable to control their phenylalanine levels with dietary treatment. The need for help with dietary treatment might also restrict the independence of people with learning difficulties. NICE recognised that people with learning difficulties might struggle with dietary treatment but there is no evidence that this has been included in the cost analysis in this consultation document.

NICE has recommended using KUVAN at a dose of 10mg/kg. I agree that clinicians in the UK will prescribe more efficiently than in the US and that an average dose of 10mg/kg is appropriate for the cost analysis. However, I believe that clinicians should be able to prescribe within the marketing authorisation, which ranges from 5mg/kg to 20mg/kg.

I believe that all people with PKU should have access to Kuvan on the NHS, and all future treatments for PKU that become available should also be funded to enable people with PKU to live freer, happier lives, and fulfil their potential.

Name	
Comments on the ACD:	
As a 24yr old woman having lived with PKU all my life I can say with complete confidence that the idea of taking a life changing drug away from a young adult at the age of 18 or any age is ludicrous. I have struggled considerably with my diet whilst leaving the comforts of home. I no longer had my mother preparing meals, ordering prescriptions, picking up prescriptions and helping me manage my PKU. After managing to secure a place at university I was petrified of the idea of attempting to live on my own with my diet. I did not succeed on many occasions. At uni I cheated…often. It is simply impossible to get it right all the time as an adult. You come home late, forget to eat at the right time, forget supplements or you have simply miscalculated how many supplements you need. Then the PKU begins to effect your success, your relationships with friends, relationships that you rely on are effected if not lost, professors notice a decline in concentration, a glazed look in your eyes, your ability to keep up with the work load diminishes. I am on an extremely demanding and intense course. PKU and university do NOT work together. During my second year at university I had to get therapy and counselling due to my lack of confidence, a loss of love for my chosen subject (due to the unobtainable organisation of diet and work) and complete decline of my mental health and wellbeing. I know I am a responder. If I had Kuvan I can guarantee that everything that I have been through and continue to experience could have been made considerably easier, in fact I probably wouldn't have had to endure it at all. I am writing an email as I simply could not answer the form due to becoming so upset. I cannot keep telling people my problems with PKU as there are so many that effect and upset me so deeply. How can anyone be expected to explain some of the things that they struggle with most in life? Why am I put in a position where I have to sit and write how I have possibly developed brain damage due to the lack of being able to access proper medication? It is simply inhumane and immoral. I have known since I was a little girl that having a family of my own was something incredibly important to me. I am now coming to a stage in my life where I want to think about this seriously. I am so scared. I am so angry that I cannot look to my future and be excited about the possibility of having a family of my own because of my PKU. It fills me with dread, the idea that I could permanently damage an unborn child due to not doing the diet perfectly. Why are women like me put in this position? who would want that for their sister, daughter, niece, granddaughter? Everything that I suffer my family also suffers. PKU does not just effect people like me it effects everyone who cares for me. Imagine how they feel helplessly watching my decline and struggles. It breaks my heart to think that I am the source of so much pain. I try to tell myself that I am not the source. Being unable to access this drug is the source. That is why I have to relive my issues so often, in some feeble attempt to access a drug which I responded to when I was just 7yrs old. This fight for Kuvan has been going on for so long I have no hope. I want that to change. I want to look to my future and not just see the risk of damaging my family, finding employment, struggling with pregnancy or losing loved ones due to the repercussions of dietary struggles. Where is the hope? Please can you give me some? I actually don't know how I am going to cope with what the future holds for me without Kuvan.	

Name	

To whom it may concern

I wish to express my sadness and annoyance at 5he NICE decision to allow Kuvan for people under 18. In its self that will help and hinder everyone who responds to Kuvan.

My own daughter, who has pku is 17. If Kuvan was made available for her tomorrow I would not want her to have it. Knowing how much it can improve her life and then have it snatched away again would be extremely cruel

All of my daughters life has been a daily struggle. Monitoring each and every thing she eats is a very difficult thing to do. Not only difficult for my daughter but difficult for me also.

She has suffered each and everyday, everyday she can't eat what she wants, when she doesn't get invites to friends parties, when she can't go to a restaurant, when she can't eat the same things at school, she has never had a school dinner. It is a struggle for her.

Its a struggle for me to watch her struggle.

We parked our car once while living in [redacted], we were going to a particular shop. We turned a corner on route just to discover there was a food festival on in the high street. I quickly said I'd forgotten something in the car. We went back and then went a different route to the shop.
Why, because I couldn't bear seeing my daughters disappointed look as she would know the lovely food smells would not be tasted. I would not be cruel enough to walk my daughter through a food festival.
That is what life is like.

I could litter this letter with similar stories.
So, giving an under 18 Kuvan and then taking it away again would be child cruelty. It would be devastating to the person.

Pku is a condition for life, it doesn't disappear at the age of 18.

I urge you to change your mind and give kuvan to everyone of any age. You have the ability to change my daughters life. I think it is cruel and despicable that you haven't already.

Please reconsider your intentions and give Kuvan to everyone.

Name	
Comments on the ACD:	

I hope you will accept my input on the Kuvan consultation despite being a little late for the deadline.

I am the friend of an adult with PKU and while we are both happy that NICE has recommended the use of Kuvan for children, I believe that patients of all ages with PKU who respond to treatment with Kuvan should have the opportunity to use this medicine to improve their quality of life.

Having seen the difficulties my friend faces not only when we go out to restaurants together, but also when cooking for herself and trying to stay healthy when travelling for her work, I believe it would make an enormous difference to her life if she had some more flexibility in how much protein she could eat. I have seen her go hungry or eat nothing but a plate of chips when everyone around her was tucking into proper meals, which really has an impact on how much she can feel part of a group or enjoy herself among other people. I know the stress of constantly being so constrained and having to expend so much effort on her diet has at times made life very difficult for her and affected her mental health.

NICE has not considered the problem of young people stopping treatment with Kuvan on their 18th birthday. Managing phenylalanine levels with dietary treatment alone is very difficult, especially for teenagers leaving home, starting work, and establishing themselves as adults in the world. 18 year-olds accustomed to a very relaxed diet through using KUVAN will not have the coping skills to switch to a strict diet which involves constant preparation of meals, precise measurement of all foods, constant management of prescriptions, regular self-administered blood tests, and difficulties in participating in social occasions based around food, including eating out in restaurants. It will lead to people not continuing the diet, being lost to treatment and having health issues related to high phenylalanine levels in adulthood. NICE has ignored this issue completely.

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NICE has not considered the harm of Maternal PKU Syndrome and the worry this can cause to women with PKU throughout their lives until the menopause. When deciding that Kuvan is not cost effective in adults, NICE has ignored the benefits to women with PKU of using Kuvan to help them have happy intimate relationships without having to worry about an unplanned pregnancy resulting in Maternal PKU Syndrome, and have safe and happy pregnancies, whether planned or not. NICE has recognised that controlling phe levels is important in early pregnancy, ideally before conception, and has recognised that this would reduce the risks of Maternal PKU Syndrome. However, the harms to mother and child from high levels in early pregnancy have not been included in the cost analysis. The mental and physical experiences of women with PKU who have gone through the pre-conception diet and a pregnancy, a time when hormonal changes and other health changes due to pregnancy are significant, have not been taken into account. Pregnancy can also result in severe illness that makes the diet even more difficult both mentally and physically. All of these difficulties and more are articulated by PKU patients in Ford,

O'Driscoll, and MacDonald, 'Reproductive Experience of Women Living with PKU', Molecular Genetics and Metabolism Reports 17 (2018), pp.64-68, which NICE needs to take into account. The hormonal changes experienced by women during the menopause should also be taken into account as more early treated adults go into middle age: women need help to ensure they can maintain low phenylalanine levels throughout life. I believe that NICE has failed to take account of the issues experienced by women with PKU and that this is a major failing in the draft guidance.
NICE has ignored that many adults with PKU who have problems associated with high phenylalanine levels – like brain fog, depression, or poor memory – simply cannot cope with dietary treatment. The NHS should not leave people without a realistic option for treatment. Also, many adults who experience difficulties were told by the NHS when they were children in the 1970s-1990s that they did not need to continue the diet in their late teenage years and in adulthood, and so didn't, trusting their clinicians. The NICE draft guidance does not take into account that they were advised in this way, and that Kuvan would help them control their phenylalanine levels.

I also believe that NICE has undervalued the work and impact that managing PKU can have on adults with PKU and their families. People with PKU spend a lot of time looking after themselves and controlling their diet, or suffering the symptoms of high phenylalanine levels. This is clear from studies such as Ford, O'Driscoll, and MacDonald, 'Living with Phenylketonuria: Lessons from the PKU Community', Molecular Genetics and Metabolism Reports 17 (2018) pp.57-63 which gives a detailed account of the lived experiences of people with PKU. Also, the draft guidance does not take into account the positive economic, health, and social impacts of having more people working and achieving more in their careers, contributing to their communities, and being more active members of society, all of which would be possible with their phenylalanine levels better controlled through the use of Kuvan and any other new treatments that are created to treat PKU.
People with learning disabilities are at a higher risk of being unable to control their phenylalanine levels with dietary treatment. The need for help with dietary treatment might also restrict the independence of people with learning difficulties. NICE recognised that people with learning difficulties might struggle with dietary treatment but there is no evidence that this has been included in the cost analysis in this consultation document.
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I believe that all people with PKU should have access to Kuvan on the NHS, and all future treatments for PKU that become available should also be funded to enable people with PKU to live freer, happier lives, and fulfil their potential.

Name	
Comments on the ACD:	

Good Afternoon, first of all can I thank you for approving the use of Kuvan for prescription to under 18 year olds.

I have a Grandson with PKU at the moment he is 8. He is on 5 exchanges a day and is constantly hungry. We don't know if he is a responder to Kuvan, he has not had a trail.
My Grandson was diagnosed at 5 days old and has always been on the diet, however even with this he still has significant learning disabilities and behavioural difficulties. He has a 1 -2-1 on class support in school. He has memory and retention difficulties.

We have heard from other children at the NSPKU conference how Kuvan has improved their concentration, digestion, stomach issues, brain got as well as increasing the amount of protein they can eat.

We know PKU is a life long condition, adults who are not on the diet have reported memory issues alongside a whole host of other side affects.

The brain does not stop firing neurons at the age of 18 most people are just going to university, learning to drive, learning employability skills. It's a time when you would be expected to be more independent, take your place in society. I think stopping Kuvan at this age would be particularly cruel and detrimental to a person's health and well being, particularly for female PKU patients who wish to have children.

PKU is such a rare condition and I can understand why there is little research into the affects of it on the brain, however I hope you will listen to the patients and the families of people who suffer with PKU and support is in providing Kuvan to patients for life.

I understand the cost implications of this, however if these patients come off Kuvan at 18 the cost in other medication/ treatments will increase.

Please help me to help my Grandson and other people with PKU.

Name	
Comments on the ACD:	

Dear TA Team 1,

I welcome the recommendation that children can use Kuvan but I believe that patients of all ages with PKU who respond to treatment with Kuvan should be able to use this medicine. I write this as a friend of an adult with PKU, who I have seen struggle with this disorder both mentally and physically. Trying to find support across the UK has been challenging, and access to this treatment has made her daily life that much easier— in that it makes an incredibly challenging disease somewhat manageable. Eating out with this friend is a constant battle of indignity, of hoping restaurants will allow for a series of side dishes instead of mains, and not protest, even when confronted with a medical diagnosis, and treatments like Kuvan have allowed my friend some dignity and space to enjoy some semblance of a normal social life.

NICE has not considered the problem of young people stopping treatment with Kuvan on their 18th birthday. Managing phenylalanine levels with dietary treatment alone is very difficult, especially for teenagers leaving home, starting work, and establishing themselves as adults in the world. 18 year-olds accustomed to a very relaxed diet through using KUVAN will not have the coping skills to switch to a strict diet which involves constant preparation of meals, precise measurement of all foods, constant management of prescriptions, regular self-administered blood tests, and difficulties in participating in social occasions based around food, including eating out in restaurants. It will lead to people not continuing the diet, being lost to treatment and having health issues related to high phenylalanine levels in adulthood. NICE has ignored this issue completely.

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NICE has not considered the harm of Maternal PKU Syndrome and the worry this can cause to women with PKU throughout their lives until the menopause. When deciding that Kuvan is not cost effective in adults, NICE has ignored the benefits to women with PKU of using Kuvan to help them have happy intimate relationships without having to worry about an unplanned pregnancy resulting in Maternal PKU Syndrome, and have safe and happy pregnancies, whether planned or not. NICE has recognised that controlling phe levels is important in early pregnancy, ideally before conception, and has recognised that this would reduce the risks of Maternal PKU Syndrome. However, the harms to mother and child from high levels in early pregnancy have not been included in the cost analysis. The mental and physical experiences of women with PKU who have gone through the pre-conception diet and a pregnancy, a time when hormonal changes and other health changes due to pregnancy are significant, have not been taken into account. Pregnancy can also result in severe illness that makes the diet even more difficult both mentally and physically. All of these difficulties and more are articulated by PKU patients in Ford, O'Driscoll, and MacDonald, 'Reproductive Experience of Women Living with PKU', Molecular Genetics and Metabolism Reports 17 (2018), pp.64-68, which NICE needs to take into account. The hormonal changes experienced by women during the menopause should also be taken into account as more early treated adults go into middle age: women need help to ensure they can maintain low phenylalanine

levels throughout life. I believe that NICE has failed to take account of the issues experienced by women with PKU and that this is a major failing in the draft guidance.
NICE has ignored that many adults with PKU who have problems associated with high phenylalanine levels – like brain fog, depression, or poor memory – simply cannot cope with dietary treatment. The NHS should not leave people without a realistic option for treatment. Also, many adults who experience difficulties were told by the NHS when they were children in the 1970s-1990s that they did not need to continue the diet in their late teenage years and in adulthood, and so didn't, trusting their clinicians. The NICE draft guidance does not take into account that they were advised in this way, and that Kuvan would help them control their phenylalanine levels.

I also believe that NICE has undervalued the work and impact that managing PKU can have on adults with PKU and their families. People with PKU spend a lot of time looking after themselves and controlling their diet, or suffering the symptoms of high phenylalanine levels. This is clear from studies such as Ford, O'Driscoll, and MacDonald, 'Living with Phenylketonuria: Lessons from the PKU Community', Molecular Genetics and Metabolism Reports 17 (2018) pp.57-63 which gives a detailed account of the lived experiences of people with PKU. Also, the draft guidance does not take into account the positive economic, health, and social impacts of having more people working and achieving more in their careers, contributing to their communities, and being more active members of society, all of which would be possible with their phenylalanine levels better controlled through the use of Kuvan and any other new treatments that are created to treat PKU.
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I believe that all people with PKU should have access to Kuvan on the NHS, and all future treatments for PKU that become available should also be funded to enable people with PKU to live freer, happier lives, and fulfil their potential.

Name	
Comments on the ACD:	

Dear Team

Children stopping Kuvan at 18 years old

As we know, the brain still will continue to develop over 18 years of age, and when you are an adult there are a lot of changes that you go through. To have to come off Kuvan and in addition to learn how to deal with a restricted protein diet + dietary supplements and also to control blood Phe levels and to deal with big changes of that sort (as well as other life changes). This will cause a number of problems as there may be some who have never had to deal with a restricted diet as they went on to Kuvan from a very young age and this could cause a lot of problems with controlling their diet and maintaining Phe levels along with studies and work. They may find that they are having problems with their mental health and other problems could arise from not being able to control levels. From focusing and organising the diet to planning what supplements or foods will be needed, and if they are not able to tolerate the food this could cause an eating disorder or digestive problems.

The required dose will need to be looked into, as some people require a different amount of the medication, whether it is higher or lower. I feel that this possibility needs to be looked into as other medication has a different dosage for different patients and not everyone is the same.

I feel a lot of information has been overlooked for stopping children at 18 years of age and think that it needs to be looked into again, as I feel that the outcome for all the children who are on Kuvan will result in a lot of problems if this is then taken away from them at 18.

Part 2
Pre con and pregnancy diet
A pre con diet (Dietary measures) should ideally be started before conception to avoid congenital effects, but at least at the earliest possible opportunity to avoid harmful effects on the unborn child. If there are high levels of phe in pregnancy this can have many harmful effects on the unborn child.

I have been on pre con and with my current pregnancy i went into hospital just to ensure all was well. Had I been on Kuvan there would not have been a problem, they were aware of the pku but were unable to manage it. They managed it the best way they were able too. As I can only have a restricted amount of protein and the meal that i was given was Jacket potato with cheese and beans. I was unable to have the cheese and beans so i just had the jacket potato. Just wanted to be able to share the difference that it would have made.
What i was given pic1 What i was able to have pic2


I feel that all pku’s should get the opportunity to have kuvan, if it will help them with pku, as you can see it is very restricted and this is also during pregnancy. There are many foods that all pku’s are unable to have, or can only a small amount of because of it being a protein restricted diet and I feel that it needs to be looked into for everyone to have kuvan as a long term treatment, if they are suitable.Il feel that no one should be told they can’t have it due to being an adult as pku affects everyone of all ages
Kind Regards

Name	
Comments on the ACD:	

I welcome the recommendation that children can use Kuvan but I believe that patients of all ages with PKU who respond to treatment with Kuvan should be able to use this medicine. I write this as a friend of an adult with PKU:

In the interests of confidentiality I am referring to my friend as "Charlie", although this is not actually her name...

I met Charlie about 5 years ago. We were both new employees at the same workplace and of a similar age (35-40ish). Charlie came across as being vivacious and seemed very eager to make new friends. Charlie explained about her condition (as she must have to do with almost every person she meets) and the limitations it puts on her day-to-day life, but she seemed determined for it not to define her. I imagine she was relishing the opportunity for a new chapter in her life and I admired her for that. We quickly became friends.

We socialised together, often going for staff drinks after work. Charlie initially joined in as much as anyone else, she is really quick witted and highly intelligent - great company and good fun. Obviously she had to limit her alcohol intake, but then there was always the question of, "should we go for something to eat?" Charlie always visibly shrunk at this stage, not wanting to make a fuss, but also knowing full-well she was going to have to deal with the "why can't you eat this or that?" conversations and the inevitable looks of incomprehension, suspicion or fatigue as to, "why is she making a fuss, it's just food?" from restaurant staff and colleagues who weren't aware of her condition. So then, again she'd have to explain herself...

This is just one example of how PKU dampens Charlie's spirit on a daily basis. Charlie also suffers from mood fluctuations and brain-fog (which can make her hard to work with or relate to at times) and sometimes she appears depressed and un-focused. I know she struggles with romantic relationships. Although she has a high sex drive, she is very hesitant about having sexual relationships because she is scared of becoming pregnant and having to deal with the challenges of pregnancy with PKU and the possibility of having to raise a child with PKU also. Dating is a hugely stressful thing for her because it is so loaded, and I can see it causes her great emotional turmoil.

Despite all of this Charlie manages her condition extremely well, she sticks to the diet religiously. She has great discipline and self-control, and as a result she is generally healthy, but I know she finds it very, very hard and very, very draining. Basically PKU rules her life.

It is desperately unfair that my friend has to continue to live a limited and anxious existence when medication exists that could drastically change her life.

In addition to this, Charlie has explained to me that NICE has not considered the problem of young people stopping treatment with Kuvan on their 18th birthday. Managing phenylalanine levels with dietary treatment alone is very difficult, especially for teenagers leaving home, starting work, and establishing themselves as adults in the world. 18 year-olds accustomed to a very relaxed diet through using KUVAN will not have the coping skills to switch to a strict diet which involves constant preparation of meals, precise measurement of all foods, constant

management of prescriptions, regular self-administered blood tests, and difficulties in participating in social occasions based around food, including eating out in restaurants. It will lead to people not continuing the diet, being lost to treatment and having health issues related to high phenylalanine levels in adulthood. NICE has ignored this issue completely.
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I also believe that NICE has undervalued the work and impact that managing PKU can have on adults with PKU and their families. People with PKU spend a lot of time looking after themselves and controlling their diet, or suffering the symptoms of high phenylalanine levels. This is clear from studies such as Ford, O'Driscoll, and MacDonald, 'Living with Phenylketonuria: Lessons from the PKU Community', Molecular Genetics and Metabolism Reports 17 (2018) pp.57-63 which gives a detailed account of the lived experiences of people with PKU. Also, the draft

guidance does not take into account the positive economic, health, and social impacts of having more people working and achieving more in their careers, contributing to their communities, and being more active members of society, all of which would be possible with their phenylalanine levels better controlled through the use of Kuvan and any other new treatments that are created to treat PKU.
People with learning disabilities are at a higher risk of being unable to control their phenylalanine levels with dietary treatment. The need for help with dietary treatment might also restrict the independence of people with learning difficulties. NICE recognised that people with learning difficulties might struggle with dietary treatment but there is no evidence that this has been included in the cost analysis in this consultation document.
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I believe that all people with PKU should have access to Kuvan on the NHS, and all future treatments for PKU that become available should also be funded to enable people with PKU to live freer, happier lives, and fulfil their potential.

Name	
Comments on the ACD:	

Dear TA Team 1,
I welcome the recommendation that children can use Kuvan but I believe that patients of all ages with PKU who respond to treatment with Kuvan should be able to use this medicine. I write this as a friend of an adult with PKU.

I participated in a challenge to raise awareness of PKU last year where I undertook the recommended diet to see how it felt to try to manage protein intake as a treatment model, and even as a 35 year old educated to doctoral level with more than an average interest in nutrition found it almost impossibly restrictive. I cannot believe that people who respond well to treatment with Kuvan would not find their lives immeasurably less restrictive, and so less stressful, if allowed to continue treatment past 18.
NICE has not considered the problem of young people stopping treatment with Kuvan on their 18th birthday. Managing phenylalanine levels with dietary treatment alone is very difficult, especially for teenagers leaving home, starting work, and establishing themselves as adults in the world. 18 year-olds accustomed to a very relaxed diet through using KUVAN will not have the coping skills to switch to a strict diet which involves constant preparation of meals, precise measurement of all foods, constant management of prescriptions, regular self-administered blood tests, and difficulties in participating in social occasions based around food, including eating out in restaurants. It will lead to people not continuing the diet, being lost to treatment and having health issues related to high phenylalanine levels in adulthood. NICE has ignored this issue completely.
NICE's analysis underestimates the benefits of KUVAN treatment for adults with PKU. NICE says there is no risk of permanent damage to the brain after the age of 18, but this is contradicted by other statements made by NICE in the document which recognise that permanent harm can occur after the age of 18 and that brain development continues until age 25. There is good evidence that many adults with PKU have very serious symptoms caused by high phenylalanine levels in adulthood. These problems in adults are undervalued by NICE. Furthermore, new research into neuroplasticity and more recently neurogenesis is showing more clearly that the brain continues to change and develop throughout life. NICE has ignored that the adult brain does not stop changing and developing.
NICE has not considered the harm of Maternal PKU Syndrome and the worry this can cause to women with PKU throughout their lives until the menopause. When deciding that Kuvan is not cost effective in adults, NICE has ignored the benefits to women with PKU of using Kuvan to help them have happy intimate relationships without having to worry about an unplanned pregnancy resulting in Maternal PKU Syndrome, and have safe and happy pregnancies, whether planned or not. NICE has recognised that controlling phe levels is important in early pregnancy, ideally before conception, and has recognised that this would reduce the risks of Maternal PKU Syndrome. However, the harms to mother and child from high levels in early pregnancy have not been included in the cost analysis. The mental and physical experiences of women with PKU who have gone through the pre-conception diet and a pregnancy, a time when hormonal changes and other health changes due to pregnancy are significant, have not been taken into account. Pregnancy can also result in severe illness that makes the diet even more difficult both mentally and physically. All of these difficulties and more are articulated by PKU patients in Ford, O'Driscoll, and MacDonald, 'Reproductive Experience of Women Living with PKU',

Molecular Genetics and Metabolism Reports 17 (2018), pp.64-68, which NICE needs to take into account. The hormonal changes experienced by women during the menopause should also be taken into account as more early treated adults go into middle age: women need help to ensure they can maintain low phenylalanine levels throughout life. I believe that NICE has failed to take account of the issues experienced by women with PKU and that this is a major failing in the draft guidance.
NICE has ignored that many adults with PKU who have problems associated with high phenylalanine levels – like brain fog, depression, or poor memory – simply cannot cope with dietary treatment. The NHS should not leave people without a realistic option for treatment. Also, many adults who experience difficulties were told by the NHS when they were children in the 1970s-1990s that they did not need to continue the diet in their late teenage years and in adulthood, and so didn't, trusting their clinicians. The NICE draft guidance does not take into account that they were advised in this way, and that Kuvan would help them control their phenylalanine levels.

I also believe that NICE has undervalued the work and impact that managing PKU can have on adults with PKU and their families. People with PKU spend a lot of time looking after themselves and controlling their diet, or suffering the symptoms of high phenylalanine levels. This is clear from studies such as Ford, O'Driscoll, and MacDonald, 'Living with Phenylketonuria: Lessons from the PKU Community', Molecular Genetics and Metabolism Reports 17 (2018) pp.57-63 which gives a detailed account of the lived experiences of people with PKU. Also, the draft guidance does not take into account the positive economic, health, and social impacts of having more people working and achieving more in their careers, contributing to their communities, and being more active members of society, all of which would be possible with their phenylalanine levels better controlled through the use of Kuvan and any other new treatments that are created to treat PKU.
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I welcome the recommendation that children can use Kuvan but I believe that patients of all ages with PKU who respond to treatment with Kuvan should be able to use this medicine. I write this as a friend of an adult with PKU, and have seen first hand the manner in which this medicine benefits them and the difficulties they as a functioning and intelligent adult have regarding dietary requirements. I can only imagine how diet only controls would be detrimental to a patient with lesser capacity or diligence.

NICE has not considered the problem of young people stopping treatment with Kuvan on their 18th birthday. Managing phenylalanine levels with dietary treatment alone is very difficult, especially for teenagers leaving home, starting work, and establishing themselves as adults in the world. 18 year-olds accustomed to a very relaxed diet through using KUVAN will not have the coping skills to switch to a strict diet which involves constant preparation of meals, precise measurement of all foods, constant management of prescriptions, regular self-administered blood tests, and difficulties in participating in social occasions based around food, including eating out in restaurants. It will lead to people not continuing the diet, being lost to treatment and having health issues related to high phenylalanine levels in adulthood. NICE has ignored this issue completely.

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I know I couldn't live on that diet and it is really restrictive - it is unfair and everyone who responds to it should be able to access it. Having a friend with the condition I see how difficult it can be ordering a meal in a restaurant for example, finding something on the menu that she can safely eat and the confusion it can cause to the staff due to unawareness of the PKU condition.

Name	
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This is my evidence of my experiences living with PKU and why KUVAN should be made available to all children and adults to allow us all to live the quality of life we deserve.

- I was born in [redacted] in 1979. I have 3 older siblings, 2 of which also have PKU and the other is a carrier of PKU. I have 41 years of first hand experience of living with PKU and trying to cope with all of the ways it has affected me, and also my brother and sister throughout those years.

- PKU was never a big issue when I was young as my mum always made sure I never felt like I was any different and always made really lovely meals. I had an amazing school cook who made PKU versions of every meal for me, I was very lucky. I was however always painfully shy and nervous, I was never an outgoing child. And even though I did encounter bullying in primary school and I never really enjoyed going, the happiness, love and fun I felt at home far out weighed the unhappy school days.
But life with PKU became harder when I was 11 and started high school.

- Shortly after starting high school, I started being bullied about my PKU (amongst other things). I endured daily insults about my 'disgusting' food, my 'stinking' supplements and that I was 'diseased' and a 'junkie' so people avoided me. I used to choose to eat my packed lunch in solitude to escape torment about my PKU in the canteen in front of everyone. Sometimes the only place I could get peace was locking myself in a toilet cubicle and sitting with my lunch on my lap sobbing as I ate, jumping every time the door opened scared to breathe incase I was caught doing so. As time went on the bullying became quite severe, it became physical as well as emotional and it was causing me anxiety so badly that I was being sick all the time which was causing havoc with keeping track of my food and supplement intake. My mental health became a real problem as I began to make myself sick a lot, it almost felt like a form of release from the real emotional pain I had inside. It became an everyday, several times a day occurrence which led to severe stomach cramping and pain. I used to scream in pain doubled up. My parents would take me to the doctor only to be told each time, and I remember hearing these words coming out of my doctors mouth like it was yesterday, "There's nothing wrong with her, she's just playing on it to get out of school" In my head I was screaming out for help but vocally I was silent because I didn't know how to communicate how I was feeling as I didn't understand it myself. I felt desperate for someone to understand and explain to me why I was the way I was. I couldn't understand why, when I was so kind, everyone was so cruel and hated me so much. My emotions were so complex and my head was in constant panic overdrive seeking a way to get out of dealing with the next day. I spent my life from 11 to 15 terrified, confused and had completely cut myself off from socialising with my peers for fear of rejection. When I was 14 I had come to a point where I didn't want to carry on going through the same mental torture every single day, I was running out of ways to get out of going to school and I just wanted it all to stop. With the bathroom door locked, I got a handful of sleeping tablets from the bathroom cabinet and a glass of water. I held them in my hand for a long time trying to find the courage to take them, then, I heard my mum and dad laughing and joking in the living room and it stopped me in my tracks, I instantly knew that if I took the tablets it would destroy them, the people who I loved most in the world and the only ones that I felt truly safe with. So I put them back in the bottle and just carried on. I had been told I'd come off diet in my teens by my dietician so I asked to come off my diet then at 14 as I thought that would solve my problems. I didn't realise back then, but coming off diet had an

even worse impact on me socially and with my anxiety, depression, concentration etc. The coming years weren't going to get any better for me.

- Moving on from high school to college. I struggled through college, being extremely nervous about socialising with my fellow students, tutors and clients (hairdressing) I struggled with the theory work, I was always much better at the practical hands on work. I did make a couple of friends there and I muddled through to finally become a qualified hairdresser, but it took me nearly an extra year to get it finished due to struggling with the theory work. I also ran into issues in the beginning with my tutor who used my extreme shyness and vulnerability to bully and humiliate me in front of the other students and clients. When she had upset me she would always tell me to stop being so sensitive that she was only joking! I always just stood there unable to say or do anything to stand up for myself through total fear of confrontation. I started to have the same feelings about going to college as I did with high school and I began making myself sick again. I only had to go to college 1 day a fortnight as it was an apprenticeship and thankfully I was really happy at my work. Eventually I spoke up and the tutor was fired as there were other girls she was doing this to. I faced issues in several of my jobs where my shy personality, inability to speak up for myself and the fear of confrontation just made people take advantage and walk all over me. My concentration, memory, anxiety and stress of not being able to stick within time frames began to become an issue at most jobs I had.

- Most of my relationships I was in from the age of around 21 had an element of control in them. My soft nature, fear of confrontation while trying to express myself during conversations plus my severe lack of confidence and self worth were always picked up on and used against me.....as were some of my cognitive issues. I would lose words during talking and it used to make my ex get impatient and angry which used to give me anxiety and panic attacks. Also my bad memory was used against me. One of my ex's used to come right up to my face and grit his teeth and tap his head in an angry manner with his finger and say "you aren't right in the head you" because I couldn't remember something he had said or I had said, then when I was upset he would start laughing and say I was too soft. This is just one of many examples of how my mental health was used against me throughout the years. Because I was told to come off diet in my teens, the high phenylalanine levels in my blood made me find it impossible to respond or stand up for myself and I would always respond in the wrong way or say the wrong thing. I used to actually believe I really was losing it.

- At the age of 31 I made the decision to go back on diet to prepare for conception, even though I can admit now, I really wasn't in the best place mentally to try for a baby. But my confidence had been completely shattered countless times and I felt like I would never find anyone else and I was scared of being alone, so I stayed in the relationship always hoping it would get better. I felt broken and worthless and thought that the way I was being treated is as good as it would get for me. I felt like I wasn't worthy of finding anyone who would treat me better and I was scared to miss my chance to be a mother. Rejection and being emotionally manipulated was always something that deeply affected me and I think I felt that having a baby would mean I would always have someone who would love me and always want me around and the emptiness I had always felt inside would go away. I wouldn't feel alone anymore. We had been trying a short while but started to go through a really bad spell and I had decided that it was the wrong time to try and get pregnant. But I then discovered I was pregnant. The worry of it being the wrong time disappeared in the excitement and I had the most amazing pregnancy. It was the first time in my life that I can honestly say that I felt truly happy and healthy,

mentally also. It was a struggle getting used to the diet at first due to being off diet for 17 years and also because when I was younger my mum was the one who handled my PKU. But I quickly got used to following it perfectly all the way through. I had my healthy little boy in May 2012 when I was 33 years old. I was told there was no need to stay on diet after the birth, so I came back off diet. It didn't take long for me to realise that coming back off diet was a huge mistake as I noticed I was having issues cognitively and this time I linked it to PKU. My depression, anxiety, memory, concentration and focus, emotions, loss of words, struggling to express myself and also the foggy and headachy feeling in my head were much worse than when I was younger and the feeling of being totally overwhelmed and unable to handle more than one thing at a time, sometimes even with just simple everyday things. I believe the drastic change in my diet was the reason for this as well as the pressure of being a first time mum with no real support. I never received any follow up appointments with the PKU clinic to check my health or how I was coping off diet. I have been trying on and off to get back on the PKU diet since then, and succeeded beginning of 2020. Becoming a mother has been one of the most amazing and also one of the most challenging things I've ever done in my life. It's getting harder to cope as a single mother with PKU as my little boy gets older. I feel the burden of so much guilt because of my bad days where I feel unwell, also because of my anxiety, he's seen me take panic attacks, days where I'm impatient and grumpy because I feel exhausted and when I'm feeling really emotional. I do my very best for him but I do tend to feel like a failure as a mother a lot, I find it hard doing it alone with out much support as well as trying to keep on top of running a house, bills, work AND managing PKU.

- Although my symptoms have improved since returning to diet beginning of 2020, I face a constant battle of staying on track with the food I eat and taking my supplements. After being told by dieticians to come off diet in my teens (where I decided to come off a little earlier than suggested) and then again after the birth of my son and being off diet for around 25 years eating a normal diet of whatever food I wanted, it is so hard to go back to such a restricted diet. It's unimaginable, unless you are living this life you will never understand the impact it has on all aspects of your life and it affects all those close to you too. Plus if I do slip up I run the risk of being confused, losing focus and words, repeating myself, stuttering, becoming forgetful, anxiety and panic attacks....some of which I can unfortunately still experience even when my levels are where they should be. Some of these symptoms are sadly just a part of who I am now. Diet is not enough!!

- Taking kuvan away from kids at 18 who have become used to life with a more relaxed diet and with all the cognitive benefits Kuvan offers, an age where they will be setting off into the world independently, living alone and moving on to either further education or working life is the worst thing that could happen to them. They will have no idea how to have control of a very low protein diet, this paired with having to drastically stop a treatment which was helping them mentally and cognitively, is going to have a real detrimental affect on their mental health. They won't be able to cope. I, as well as many other adults with PKU know how hard this is going to be for them as this is our reality every single day!

- I was failed by so many medical professionals all through my life, my doctor when I was a child who said there was nothing wrong with me when I was riddled with anxiety, my dietician in my teens who allowed me off diet, my dietician after the birth of my child advising me to go back off diet and my dietician I had while trying to get back on diet over the last 4 or 5 years for giving me absolutely no support at all, I got back on diet myself. I know there are so many other adults who have been through similar experiences, including my sister and brother.

Please don't fail PKU adults again! We all need to be allowed access to Kuvan!!

- We should not be left to manage PKU with a severely restricted diet alone when there have been treatments specially developed for our condition. Treatments that people all over Europe and America have had access to for 12 years!!!
- My experiences with PKU is exactly the kind of life that will be inflicted upon all these children when Kuvan is taken away from them when they turn 18!

- KIDS NEED LIFETIME ACCESS TO KUVAN!!

- ADULTS NEED LIFETIME ACCESS TO KUVAN!!

- PKU doesn't disappear when we get to 18 years old. This is when life begins to be more challenging and that's when the real problems are just getting started!

Yours Sincerely

Name	
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I welcome the recommendation that children can use Kuvan but I believe that patients of all ages with PKU who respond to treatment with Kuvan should be able to use this medicine. I write this as a cousin of a person living with PKU and witnessing firsthand the restrictive nature of this diet.
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NICE has ignored that many adults with PKU who have problems associated with high phenylalanine levels – like brain fog, depression, or poor memory – simply cannot cope with dietary treatment. The NHS should not leave people without a realistic option for treatment. Also, many adults who experience difficulties were told by the NHS when they were children in the 1970s-1990s that they did not need to continue the diet in their late teenage years and in adulthood, and so didn't, trusting their clinicians. The NICE draft guidance does not take into account that they were advised in this way, and that Kuvan would help them control their phenylalanine levels.

I also believe that NICE has undervalued the work and impact that managing PKU can have on adults with PKU and their families. People with PKU spend a lot of time looking after themselves and controlling their diet, or suffering the symptoms of high phenylalanine levels. This is clear from studies such as Ford, O'Driscoll, and MacDonald, 'Living with Phenylketonuria: Lessons from the PKU Community', Molecular Genetics and Metabolism Reports 17 (2018) pp.57-63 which gives a detailed account of the lived experiences of people with PKU. Also, the draft guidance does not take into account the positive economic, health, and social impacts of having more people working and achieving more in their careers, contributing to their communities, and being more active members of society, all of which would be possible with their phenylalanine levels better controlled through the use of Kuvan and any other new treatments that are created to treat PKU.
People with learning disabilities are at a higher risk of being unable to control their phenylalanine levels with dietary treatment. The need for help with dietary treatment might also restrict the independence of people with learning difficulties. NICE recognised that people with learning difficulties might struggle with dietary treatment but there is no evidence that this has been included in the cost analysis in this consultation document.
NICE has recommended using KUVAN at a dose of 10mg/kg. I agree that clinicians in the UK will prescribe more efficiently than in the US and that an average dose of 10mg/kg is appropriate for the cost analysis. However, I believe that clinicians should be able to prescribe within the marketing authorisation, which ranges from 5mg/kg to 20mg/kg.

I believe that all people with PKU should have access to Kuvan on the NHS, and all future treatments for PKU that become available should also be funded to enable people with PKU to live freer, happier lives, and fulfil their potential.

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Comments on the ACD:	

Dear TA Team 1,

I welcome the recommendation that children can use Kuvan but I believe that patients of all ages with PKU who respond to treatment with Kuvan should be able to use this medicine. I write this as a friend of an adult with PKU...

NICE has not considered the problem of young people stopping treatment with Kuvan on their 18th birthday. Managing phenylalanine levels with dietary treatment alone is very difficult, especially for teenagers leaving home, starting work, and establishing themselves as adults in the world. 18 year-olds accustomed to a very relaxed diet through using KUVAN will not have the coping skills to switch to a strict diet which involves constant preparation of meals, precise measurement of all foods, constant management of prescriptions, regular self-administered blood tests, and difficulties in participating in social occasions based around food, including eating out in restaurants. It will lead to people not continuing the diet, being lost to treatment and having health issues related to high phenylalanine levels in adulthood. NICE has ignored this issue completely.

NICE's analysis underestimates the benefits of KUVAN treatment for adults with PKU. NICE says there is no risk of permanent damage to the brain after the age of 18, but this is contradicted by other statements made by NICE in the document which recognise that permanent harm can occur after the age of 18 and that brain development continues until age 25. There is good evidence that many adults with PKU have very serious symptoms caused by high phenylalanine levels in adulthood. These problems in adults are undervalued by NICE. Furthermore, new research into neuroplasticity and more recently neurogenesis is showing more clearly that the brain continues to change and develop throughout life. NICE has ignored that the adult brain does not stop changing and developing.

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Dear TA Team 1, I welcome the recommendation that children can use KUVAN but I believe that patients of all ages with PKU who respond to treatment with KUVAN should be able to use this medicine. I write this as a friend of an adult with PKU; indeed, I have close-at-hand experience of the impact that PKU can have on a patient's life as I lived with this friend for approximately two years while we were at university. This allowed me to gain a closer insight into what it means for a PKU patient living independently to manage their condition while also coping with the same, often stressful issues that students without the condition have to go through.	

Most notably, I observed that there is rarely any such thing as a relaxed food-related experience for PKU patients: every item of food made at home has to be carefully considered, weighed and in some cases even made from scratch. Dining out means choosing restaurants carefully and having often difficult conversations with people who do not fully understand the condition or have even heard of it. As someone with many allergies, I appreciate the difficulty of finding suitable food on one level, but my experience pales in comparison - allergies are now a high-profile issue for restaurants, for instance, and my symptoms are only ever temporary, as compared with the permanent impact that PKU can have.

To take the two examples of food at home that I remember most clearly, my friend spent considerable time baking her own bread using prescription flour, and was required to consume copious quantities of supplementary vitamins and minerals in the form of an unpleasant drink to make up for the restrictions in her diet; she often had to carry the pouches with her during her day-to-day activities. All this was scheduled around a heavy course load, and I was often aware of the impact that this could have on her mood and energy levels. She was simply unable to benefit from the kinds of food-based experiences that many of us take for granted, such as picking up a loaf of bread or buying some chips on the way home, and the fatigue and mood-related effects she felt also had an impact on her daily experiences. My friend is diligent in all aspects of her life and manages her diet extremely carefully, but I believe that she deserved the opportunity to relax like any other student.

We have kept in regular contact and visited one another often since our university days, and what I have often observed is that my friend has had to work through the same rigid routine in all that time (it is worth noting at this point that we began university together back in 2001). A development such as KUVAN has the potential to be a life-changing opportunity for her and adults like her. My friend has accomplished a lot in her life, but this does not mean that there is no need for her to be given an opportunity like this. As an example, she has always expressed a wish to travel but is aware of the logistical difficulties that PKU brings with this: finding pharmacies; arranging prescriptions; packing medicines; all things that those without the condition don't have to think about. KUVAN could potentially mean the ability to increase her daily protein intake almost sevenfold, but even doubling it would have a huge impact and give her even more possibilities to take advantage of. I firmly believe that it has the potential to improve her quality of life.
NICE has not considered the problem of young people stopping treatment with KUVAN on their 18th birthday. Managing phenylalanine levels with dietary treatment alone is very difficult, especially for teenagers leaving home, starting work, and establishing themselves as adults in the world. 18 year-olds accustomed to a very relaxed diet through using KUVAN will not have the coping skills to switch to a strict diet which involves constant preparation of meals, precise measurement of all foods, constant management of prescriptions, regular self-administered blood tests, and difficulties in participating in social occasions based around food, including eating out in restaurants. It will lead to people not continuing the diet, being lost to treatment and having health issues related to high phenylalanine levels in adulthood. NICE has ignored this issue completely.
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I believe that all people with PKU should have access to KUVAN on the NHS, and all future treatments for PKU that become available should also be funded to enable people with PKU to live freer, happier lives, and fulfil their potential.

Name	
Comments on the ACD:	
PKU consultation As a parent with a child who suffers from PKU I am frankly confused at the idea of withdrawing the drug at 18. My child eats different pasta, breads etc and they are quite unpalatable to to someone who is used to the usual flavours. Following the PKU diet uses a lot of maths and restraint and I 100% believe that for an adult to be successful at this diet they would need to learn how to prepare these special foods and calculate their phe content. How do you propose someone just starts on their 18th and never eats any of their favourites again? I have researched the effects of PKU that is not managed well by diet restriction on adults and the list is exhaustive and is very linked to their brain, much like children. High risks of depression and suicide compared to their peers without the condition. This is obviously a need for this drug as you can imagine as parent I am terrified of my child getting to 18 and losing medical support.	

Name	
Comments on the ACD:	
Dear TA Team 1, I welcome the recommendation that children can use Kuvan but I believe that patients of all ages with PKU who respond to treatment with Kuvan should be able to use this medicine. I write this as a friend of an adult with PKU and having observed the difficulties they experience in constantly managing a strict PKU diet. It requires constant motivation, and a great deal of support and resilience in order to maintain their mental well-being. NICE has not considered the problem of young people stopping treatment with Kuvan on their 18th birthday. Managing phenylalanine levels with dietary treatment alone is very difficult, especially for teenagers leaving home, starting work, and establishing themselves as adults in the world. 18 year-olds accustomed to a very relaxed diet through using KUVAN will not have the coping skills to switch to a strict diet which involves constant preparation of meals, precise measurement of all foods, constant management of prescriptions, regular self-administered blood tests, and difficulties in participating in social occasions based around food, including eating out in restaurants. It will lead to people not continuing the diet, being lost to treatment and having health issues related to high phenylalanine levels in adulthood. NICE has ignored this issue completely. NICE's analysis underestimates the benefits of KUVAN treatment for adults with PKU. NICE says there is no risk of permanent damage to the brain after the age of 18, but this is contradicted by other statements made by NICE in the document which recognise that permanent harm can occur after the age of 18 and that brain	

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NICE has not considered the harm of Maternal PKU Syndrome and the worry this can cause to women with PKU throughout their lives until the menopause. When deciding that Kuvan is not cost effective in adults, NICE has ignored the benefits to women with PKU of using Kuvan to help them have happy intimate relationships without having to worry about an unplanned pregnancy resulting in Maternal PKU Syndrome, and have safe and happy pregnancies, whether planned or not. NICE has recognised that controlling phe levels is important in early pregnancy, ideally before conception, and has recognised that this would reduce the risks of Maternal PKU Syndrome. However, the harms to mother and child from high levels in early pregnancy have not been included in the cost analysis. The mental and physical experiences of women with PKU who have gone through the pre-conception diet and a pregnancy, a time when hormonal changes and other health changes due to pregnancy are significant, have not been taken into account. Pregnancy can also result in severe illness that makes the diet even more difficult both mentally and physically. All of these difficulties and more are articulated by PKU patients in Ford, O'Driscoll, and MacDonald, 'Reproductive Experience of Women Living with PKU', Molecular Genetics and Metabolism Reports 17 (2018), pp.64-68, which NICE needs to take into account. The hormonal changes experienced by women during the menopause should also be taken into account as more early treated adults go into middle age: women need help to ensure they can maintain low phenylalanine levels throughout life. I believe that NICE has failed to take account of the issues experienced by women with PKU and that this is a major failing in the draft guidance.
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To whom it may concern,
I welcome the recommendation that children can use Kuvan but I believe that patients of all ages with PKU who respond to treatment with Kuvan should be able to use this medicine. I write this as a friend of an adult with PKU. I have seen first hand how difficult the diet can be and how restricting both when out and trying to cook for it.
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Dear TA Team 1,

I welcome the recommendation that children can use Kuvan but I believe that patients of all ages with PKU who respond to treatment with Kuvan should be able to use this medicine. I write this as a friend of an adult with PKU, having seen the effects of the condition on their daily life since I have known them. The complex and strict diet required in order to manage the condition is something they have to consider every day, planning meals and grocery shopping to ensure keep their protein consumption very low and avoid aspartame; food has to be carefully prepared and when certain foods or ingredients are unavailable this is much more of a problem than it would be for most people. Social events with food and drink are likewise often challenging. The 'admin' of dealing with diet and other aspects of managing this condition (e.g. arranging blood tests) can be very time-consuming and mentally taxing, and if their dietary balance/treatment is slightly off, the effects on working memory (brain fog) and mental health can be extremely stressful.

NICE has not considered the problem of young people stopping treatment with Kuvan on their eighteenth birthday. Managing phenylalanine levels with dietary treatment alone is very difficult, especially for teenagers leaving home, starting work, and establishing themselves as adults in the world. Eighteen-year-olds accustomed to a very relaxed diet through using KUVAN will not have the coping skills to switch to a strict diet which involves constant preparation of meals, precise measurement of all foods, constant management of prescriptions, regular self-administered blood tests, and difficulties in participating in social occasions based around food, including eating out in restaurants. It will lead to people not continuing the diet, being lost to treatment and having health issues related to high phenylalanine levels in adulthood. NICE has ignored this issue completely.

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NICE has ignored that many adults with PKU who have problems associated with high phenylalanine levels – like brain fog, depression, or poor memory – simply cannot cope with dietary treatment. The NHS should not leave people without a realistic option for treatment. Also, many adults who experience difficulties were told by the NHS when they were children (between the 1970s and 1990s) that they did not need to continue the diet in their late teenage years and in adulthood, and so didn't, trusting their clinicians. The NICE draft guidance does not take into account that they were advised in this way, and that Kuvan would help them control their phenylalanine levels.
I also believe that NICE has undervalued the work and impact that managing PKU can have on adults with PKU and their families. People with PKU spend a lot of time looking after themselves and controlling their diet, or suffering the symptoms of high phenylalanine levels. This is clear from studies such as Ford, O'Driscoll, and MacDonald, 'Living with Phenylketonuria: Lessons from the PKU Community', Molecular Genetics and Metabolism Reports 17 (2018) pp.57-63which gives a detailed account of the lived experiences of people with PKU. Also, the draft guidance does not take into account the positive economic, health, and social impacts of having more people working and achieving more in their careers, contributing to their communities, and being more active members of society, all of which would be possible with their phenylalanine levels better controlled through the use of Kuvan and any other new treatments that are created to treat PKU.
People with learning disabilities are at a higher risk of being unable to control their phenylalanine levels with dietary treatment. The need for help with dietary treatment might also restrict the independence of people with learning difficulties. NICE recognised that people with learning difficulties might struggle with dietary treatment but there is no evidence that this has been included in the cost analysis in this consultation document.
NICE has recommended using KUVAN at a dose of 10mg/kg. I agree that clinicians in the UK will prescribe more efficiently than in the US and that an average dose of 10mg/kg is appropriate for the cost analysis. However, I believe that clinicians should be able to prescribe within the marketing authorisation, which ranges from 5mg/kg to 20mg/kg.
I believe that all people with PKU should have access to Kuvan on the NHS, and all future treatments for PKU that become available should also be funded to enable people with PKU to live freer, happier lives, and fulfil their potential.

Name	
Comments on the ACD:	
Dear Sir/ Madam, I am writing to you to tell you my story of having and suffering with PKU. I was born in [redacted], myself and my brother where the first babies to be born with pku in the hospital. We lived [redacted], we then moved to [redacted]. By then i was 2 my mum found it very hard with two pku's as nobody have ever heard about it.	

When i was 3 my mum and dad split up and we still lived [redacted] i was having trouble taking my supplement and i ended up in hospital as my levels was sky high and as you know it is very dangerous for a child under 18 to have high levels. I was in for weeks due to the lack of supplements i was having i lost all my hair, my bones didn't grow properly and i was very weak. In the end the nurses made me sit at their desk drinking my supplement with water in and a straw, as they had already tried syringing it down. I sat there for hours through the night. Still to this day that is how i take my supplement through a straw and mixed with water. My hair eventually grew back through the year but it is awfully thin, my first toes are smaller than the rest of them also my thumbs are small. This led to embarrassment in later life.

After living in [redacted] my mum met my step dad who [redacted], we moved to numerous [redacted] throughout the years. It was very hard trying to get low protein foods as [redacted] had a price limit so we were only allowed the basics which was bread , pasta, pizza bases and calogen for milk.

As the years went i knew i was different to everyone else , when at school all the other kids had different bread and was eating chocolate , cakes and stuff i couldn't understand why i couldn't.
My primary school years was ok didn't have a problem ; the problems began in high school.

Starting high school was nervous enough but knowing i have this pku on top i hated it. i still didn't understand fully what i had, and when eating my packed lunch i started to get bullied because i had different foods to everyone else.
With this going along i felt down and depressed and i would secretly eat, so i would have my breakfast before i left the house then not eat anything till i got home. i would get home and eat my pack up in my bedroom on my own.
When i turned 16 years old i got told by the dietitian that it was safe for me to come off the diet, so i did and although i didn't eat meat , eggs or dairy i had everything else just so i can fit in. As my brother and i was on calogen for all those years no dietitian told us how many calories was in it. So, we were having it in our tea, cereal and the odd milkshakes, this led to our weight to shoot up which made myself to have more issues with confidence and self-esteem.

Just before leaving school, I had certain event happen to me in my life that was life changing when i was 16, which i will not go into detail but on top of how i was feeling with this i felt very alone in the world and felt i was the only pku in the world. Being off the diet i started to create brain fog, and a pressure in my head. I couldn't tolerate stress and people and i was very moody and just couldn't handle life. I had no one to talk to about how i was feeling and felt very suicidal i had no control of life any more.

When i turned 17 we moved to [redacted], i hated it but i felt lost and very alone, i had been working since i was 15 years old so working life had already started. Years went on and i moved out at 19years old with a friend in to a new apartment, it was ok but again i was still off the diet and my symptoms of depression were getting worse. I would sleep most of the day when i wasn't at work, and i wouldn't feel myself but really i didn't even know who i was. The last 6 months of being there my friend and i fell out and she left me with the apartment. I was hurt and upset and just didn't want to live anymore i couldn't figure out why i felt like this , i was breaking out in eczema and had terrible shakes. I felt very suicidal after this event i took myself to the doctors and they diagnosed me with clinical depression, i got referred to a councillor and was put on tablets.

I had 2 sessions of counselling but didn't got after that as i felt in myself i wasn't ready and they wouldn't understand.
I eventually moved back home.

A year had gone by and i met my ex-husband. I still wasn't on the diet, and time went on we moved in together when i was 21years old. Although i still wasn't eating any meat i was having everything else, a normal vegetarian diet, i felt my symptoms getting worse.
I found it hard to sleep, i suffered with headaches and migraines. As time went on by and we got married 2014 and i really wanted to start a family, so i knew i had to try and get back on the diet but i just didn't know how.
I eventually got back in contact with the dietician and got put through to one at [redacted] Hospital. i had all these feeling and emotions and on top of all this all the symptoms of being off the diet. I managed to get a plan and tried to get everything and i didn't realise all the food items was on offer i felt like i was living in the dark ages, i just couldn't believe it.
A couple years went on and i knew there was something very wrong with me, the number of times i attempted and failed was getting ridiculous. My weight had gone up so much due to my relationship issues and my husband was controlling, i truly thought i was losing my mind.
My work life started to struggle and i started to drink before work i felt alone and the struggles i was having was just too much. Having high levels when at work is horrendous i lose lack of concentration and i can't tolerate stress, and just get very agitated. decided to join slimming world to lose weight, i thought maybe i would feel better in myself. I managed to lose 3stone although i felt thinner i started to have major issues, my hair started to fall out, and i started to have trouble with my speech and getting out my sentences. I felt i couldn't control it , my thoughts, my head. My relationship had started to fail on my side i was always blamed for my pku and i had pressure of wanting a baby. i was 27 and i still have no child. I started to think what was i doing here why was i alive.
I decided to go to the NSPKU Conference , i had not been since i was a child. I made the journey on my own as my ex-husband would not come with me and there was no support there. I was determined to do this journey on my own. For the first time in years i manage to get my levels down for the first time. A year went on and i realise that my relationship wasn't going anywhere and what i wanted most of all was a baby and i knew i wasn't going to get one with the relationship i was in. I ended our marriage in 2019, after years of mental abuse, and having the blame for my moods, stress and pku enough was enough. I knew i wasn't to blame for this and all the years i struggled controlling my thoughts, headaches, migraines, lack of sleep and also having the pressure of trying to get back on the diet. I knew i had to seek help asap. I also ended up having an eating disorder and bulimia, which i had counselling for and sent on the right track.

I got back in contact with the dietitians at [redacted] Hospital and had a face-to-face appointment and told them about everything currently trying to get back on track. I have days where stress gets too much and i struggle day to day as the damaged has been done. The consultants and dietitians have told us we should have never been told to come off the diet. This has angered me and the whole PKU adult community because if we had the information on this from the start, we would of never of come off the diet.

Now in my current situation today i have met my partner and we are now planning to have a baby in the new year, so i am desperate to get my levels down as i am now 33 years old. I find it so hard to maintain them due to lack of food i am getting. As GP's aren't aware of PKU, they feel that it is not important and as the food is so

expensive to get, they think it doesn't matter. I put an order in and i have to wait weeks for my food, by then i have ran out and my blood levels got higher and higher. It is like a no ending circle, and feels like i am hitting a brick wall all the time.
I wake up most mornings with headaches and brain fog, and just the feeling of being un well, i feel frustrated and stressed out. As i am trying to get my levels down still i feel like i am failing all the time and my biggest fear is never being able to have a baby due to the lack of food i am getting due to companies thinking PKU not important just because they don't understand it.

This amazing drug Kuvan would help the adult community so well, it would help us have a life and live it to the fullest rather than struggling every day and stop us becoming disheartened every time we fail due to food issues and struggling in life in general.
This drug would help me so much i would have the hope that i can get my levels down and finally after all these be able to have the chance to have a family. Not just that but to just feel better in myself, to feel normal is what we all want and need, and to feel a part of life.

Thank you for reading my story

I hope this decision does change so it will give all of PKU adults a chance to live a normal life and to feel better.

Name	
Comments on the ACD:	

Re: ID1475 Sapropterin Consultation

To whom it may concern

I would be grateful if you could consider my comments from the draft NICE guidelines for the Sapropterin consultation.

My interests in this area are as follows. I am a member of the NSPKU. My spouse has PKU and has been on diet continuously since birth. At age 53, he is from the first generation of patients to have been successfully treated through dietary management. He has had a good outcome and enjoys a professional career. My comments are from the perspectives of witnessing daily dietary management of PKU, and from meeting a variety of PKU patients with different outcomes, challenges and treatment regimes through the 23 years in which I have been involved in the society.

Although I welcome the recommendation for making Sapropterin available for children, I am concerned about the recommendation against availability for adults and for pregnant women. Children become adults, who may later become maternal PKUs. To consider each group separately from the point of view of cost effectiveness does not, in my opinion, present a coherent approach.

Consider the case of a PKU patient at age 18 if Sapropterin is discontinued. At this point, the patient may be transferring from child to adult services and moving to an adult clinic. This could represent a discontinuity in care and a risk that the patient may drop out of care. As a worst case, they may decide not to participate in the diet, but not continue to be followed up by the clinic. Since 1994, it has been advocated that PKU patients should be on diet for life or treatment throughout life. This would represent a significant potential point of failure for this long-established treatment regime.

The impact on the patient's life also should be considered. This is a time in which the patient may be leaving home, thinking about employment or study, and would have to contend with learning to manage a restricted diet in addition to this. This again presents a risk that the patient may decide that it is easier to discontinue a treatment or dietary regime. Moving from Sapropterin to a diet would restrict protein intake significantly. Talking in terms of mg of protein is an abstract concept. A more effective way is to consider the impact on life choices. Typical decisions for life (both major and more trivial), such as whether to travel for holidays or work, where and what to study, whether to apply for a job, whether to go out and join family or friends for a social occasion or meal out, would require the answer to one overriding question before they could even consider the options:

"Would I be able to eat?"

In my experience of being in a relationship with a PKU patient for 23 years, the first consideration for every day is planning of meal times. My partner, incidentally, can tolerate more protein than many of his peers and therefore has a relatively relaxed regime in comparison.

There are added concerns about how potential partners may react to the condition and how this would impact on their life together. For women who may wish to have children, dietary management would become even more critical, with extremely rigorous controls on protein levels. The question above becomes even more critical when the safety and wellbeing of the unborn child is taken into account. Anecdotally, I am aware of several women of my husband's generation who have deliberately taken the decision not to have children for this reason.

In order to support the transition into dietary management at adulthood rather than childhood, what additional support would be required in the clinic? Would clinics have the resources available to deliver this and if not, what would be the additional

funding requirement? Is this something that has been factored into the cost analysis for Saproterin? If not, should it be included?
I would also suggest that a cost penalty could be quantified or considered, based on the lost potential (to themselves and the economy) of PKU patients who decide against certain life opportunities (e.g. university study) due to the complications of dietary management.
My final point concerns maternal PKU. I recognise that the review has found that the model presented is not suitable. However, I would suggest that this is treated with a matter of urgency. Sapropterin is already licensed for use in pregnancy where there are problems with control of phenylanine levels through diet alone. The extreme strict nature of the maternal diet, particularly in early pregnancy, highlights the need for this safety mechanism.
In summary, I propose that a child who is prescribed Sapropterin should be able to continue this treatment into adulthood and that it should be also made available for maternal PKUs. The recommendations as they stand are flawed. I urge the committee to review and revise their evidence and revisit the proposals.

Name	
Comments on the ACD:	

RE: Appraisal for Sapropterin for treating Phenylketonuria (PKU)
I welcome the recommendation that children will be able to access Kuvan via the NHS but I believe that all patients of all ages with PKU who respond to Kuvan should be able to use this medicine on the NHS.
The Appraisal Consultation Document issued in February 2021 does not take into account a number of important issues regarding treatment with Kuvan, PKU itself, and the current 'diet only' treatment. NICE has most definitely not taken into account all relevant evidence, especially that of PKU patients themselves. It has also seemingly ignored a large body of scientific evidence about PKU patients and their experiences, particularly that presented at earlier stages by the National Society for PKU. The recommendations are not sound and are in no way a suitable basis for guidance to the NHS and I believe NICE has most certainly not made sure that it avoids unlawful discrimination. My response should be understood as a 38-year-old educated to doctoral level with classic PKU, whose diet comprises 9g protein per day. I therefore have 38 years of lived experience being treated with the diet primarily by my family as a child and then self-administering it as an adult.
Proposal to cease treatment with Kuvan When Patients Turn 18
NICE has in no way considered the problem of young people stopping treatment with Kuvan on their 18th birthday. Managing phenylalanine levels with dietary treatment alone is very difficult. It is dependent on having parents who administer the diet correctly when the patient is a child, as mine did for me, and learning the diet from them, with the support of clinicians who can advise from afar.

NICE has not taken into consideration that children who have been on Kuvan since infancy will not have learnt the skills to self-administer the diet to the same degree as someone treated by diet alone during infancy, nor will their parents have learnt these skills, meaning they will not have an important source of support and understanding of the diet and its difficulties. NICE has also not taken into account that all those skills will have to be introduced at age 18 and will be an incredible – and probably impossible – burden for most if not all 18 year olds to take on, especially at a time when teenagers are leaving home, starting work, and establishing themselves as adults in the world. Quite simply, young people used to a relaxed diet through using KUVAN will not have the coping skills to switch to a

strict diet which involves doing for themselves what my parents did for me as a child and what I do for myself now having learnt from them. This includes but is not limited to:

- constant shopping for and preparation of suitable meals
- precise measurement of all foods and drinks such as milk
- planning one's life around food – ensuring you have enough low-protein food when you go out, negotiating eating safely and according to the diet at a place of education or work, and in social settings where you are not in control of what food is being offered
- constant management of prescriptions - which are often not filled correctly by GPs and not necessarily ordered correctly by pharmacists (see Ford S, O'Driscoll M, MacDonald A.Prescribing issues experienced by people living with phenylketonuria in the UK. Molecular Genetics and Metabolism Reports 2019; 21 100527)
- regular self-administrated blood tests, at least monthly and several times a week for women on pre-conception diet – and it is worth remembering here there is still no home-testing kit that is available to people with PKU so they can monitor levels in real time
- attending regular hospital appointments and staying in touch with dieticians to modify the diet if high phe levels are found
- constantly having to explain the diet to friends, co-workers, serving staff, and medical professionals who know less about it than you as the expert patient
- constantly advocating for yourself, especially to medical professionals when prescriptions are refused or messed up, and also to hospitality staff, who sometimes can be extremely hostile or uninterested in accommodating the PKU diet
- explaining the diet, and the implications for women in relation to Maternal PKU Syndrome, to people (including, as adults, new partners) which is emotionally exhausting
- advocating for yourself to bodies like NICE, which is especially tiring when evidence already available in the public domain has clearly not been understood or considered properly

As this list indicates, NICE has also not taken into consideration the emotional burden of the diet for all PKU patients. My life is shaped around my diet, and there is no other option. It takes up so much time and causes me so much anxiety, robs me of so much spontaneity in life, and has meant that I have not done what I would really like to do in life. I constantly have to think about what I have eaten and what I will eat, all day, every day, and plan my life accordingly. I have to make sure that if I go out I have things I can eat and my protein substitute, because I cannot rely on suitable food being available around me, or what happens if I get delayed and don't have anything with me, or if plans change suddenly. 80% of supermarket food is not suitable for people with PKU, and I often struggle to find suitable things beyond fruit and crisps if I am out and have not brought lunch with me. This is especially a struggle when I am travelling for meetings as part of my job, and the unpredictability of meeting times and lengths can have effects on my phe levels if I do not have food immediately to hand. If I do go out to eat at a restaurant I have to ensure there is something I can eat, which curtails my social life and means I am constantly revealing and explaining my health status to co-workers, friends, and dates – and usually the only thing on the menu that I can eat is chips and salad or vegetables, because everything else is meat-based or either vegetarian and made with cheese and pastry or vegan and includes pulses, nuts, and tofu. Eating out

often another source of anxiety rather than a treat or a pleasure; most recipe books and cooking programmes are largely full of things I cannot make. The PKU diet makes me feel socially isolated from my peers and from the rest of society, and has a negative impact on my life day to day.

It is *exhausting* to manage the diet constantly, and build my work, hobbies, and relationships around it so that I can continue to live independently, carry on having a good job, and have friendships and relationships. The diet also means that I have to plan holidays like military operations to ensure that I have all my low protein foods and protein substitutes, which run into the kilograms in weight for even just a couple of weeks away , and that the country I am going to will have a cuisine that includes things I can buy and eat easily – and even then it is difficult to explain the diet. I have sat in a restaurant in Athens in 2018 and been refused service when I was really hungry because I could only eat a couple of side dishes and they wouldn't let me stay unless I ordered a main course, none of which I could have. By the end of the night I was in tears. I have sat in a pub with my entire department at work when we were having Christmas Dinner in 2019 and watched them eat their main course when I didn't have anything because the person taking the booking didn't pass on the message that I had special dietary requirements so they didn't have anything I could eat. I was eventually presented with a plate of white rice and broccoli. I've always wanted to go backpacking and travel the world, including Asia and Africa, potentially working abroad as a journalist covering conflicts – but I can't travel spontaneously when I have to take kilograms worth of protein substitutes and low-protein food with me, and measure my food precisely every day, and can't be posted anywhere where supplies would be unreliable. PKU robs me of many joys others take for granted in life. I have a PhD but it took me an extra year, which my GP signed off because of my anxiety, which was caused by trying to manage my diet and such a significant project as a thesis, as well as just try to live and grow as a young person. I have cried in front of my GP years later after reading the NSPKU's Survey Results, which I took part in and which have now been translated into two important studies that show just how difficult PKU and the diet is for many patients (Ford S, O'Driscoll M, MacDonald A. Living with Phenylketonuria: Lessons from the PKU community.
Molecular Genetic and Metabolism Reports 2018; 17:57-63 and Ford S, O'Driscoll M, MacDonald A. Reproductive Experience of Women living with PKU; Molecular Genetics and Metabolism Reports 17 (2018) 64–68)**.** I am not alone in my experiences of constant high anxiety and finding the diet difficult and something that life has to revolve around. The results of the NSPKU's survey make clear the extremely difficult burden the diet is and the significant impact it has on adults' lives and NICE does not appear to have taken this evidence into account at all.

The time and energy I have to put into my diet and the way it curtails what I can do in life on micro and macro level means that I simply cannot contemplate a more high-powered career, earning more money and paying more in tax. If all PKU patients who responded to it had Kuvan throughout life, they would potentially be able to contribute more economically and socially to this country. NICE has ignored this in its modelling.

NICE has also not taken into consideration the fact that children used to Kuvan would not have grown up being used to the low-protein food that comprises a significant portion of the PKU diet treatment, nor the protein substitutes that are essential to the diet. The low-protein foods are often high in carbohydrates and sugar, bland, and difficult to cook with. The protein substitute (across brands and forms) is extremely unpalatable (it often makes me retch, and I have been known to throw up taking it), it makes breath smell, and its acidity, combined with the amount of sugar I necessarily have to have in my diet is, I believe, probably a significant contributing factor to the numerous dental fillings and two crowns I already have. Many people with PKU report similar dental issues – which of course

cost the patient (if private) or the NHS money to rectify. NICE has not taken this into account in its economic analysis either.
To assume that 18 year olds would move onto this highly restrictive diet which is so unpalatable and curtails the amount of natural protein that can be eaten in comparison to being on Kuvan, as well as the extremely significant way in which the diet curtails a PKU patient's life, is utterly ignorant of what the diet is really like. This diet is not like Weight Watchers –it excludes around 85% of foods, it is for life, it is not optional, and the alternative is that the young person ends up with high phe levels and the numerous significant symptoms that come with them. Stopping Kuvan at 18 years old will mean that lots of young people who will potentially be able to contribute to society in the ways they would otherwise be able to – including economically – and will simply do not follow any treatment for PKU and not fulfil their potential. They will also be left struggling with all the difficulties and curtailment of life that high phe levels and their symptoms entail. NICE has not factored into their analysis this loss of potential, and the cost of the NHS treating the young people who will have had Kuvan taken away from them.

NICE's Undervaluation of Adults Being Treated with Kuvan

NICE's analysis underestimates the benefits of Kuvan treatment for adults with PKU. I find it particularly worrying that NICE suggests stopping Kuvan at the age of 18 in its draft guidance but then on p. 6 of the document states that 'brain development does not stop until about age 25'. This contradictory statement is illustrative of the extremely misguided understanding of PKU and quite frankly the poor logic of the whole appraisal consultation document. It also does not take into account that neuroscience is showing that the adult brain continues to change and develop throughout life, including throughout adulthood, through structural and functional neuroplasticity and also neurogenesis. There is good evidence that many adults with PKU have very serious symptoms caused by high phenylalanine levels in adulthood: see, for example, the quotes from and results of the survey discussed in Ford S, O'Driscoll M, MacDonald A. Living with Phenylketonuria: Lessons from the PKU community. Molecular Genetic and Metabolism Reports 2018; 17:57-63). These include brain fog, depression and poor memory, all of which I have experienced even when on diet as my phe levels can fluctuate due to illness, my menstrual cycle, or simply mis-calculating or being given the wrong food or drink and inadvertently having it (mostly instances where I have been given a drink which I have later found out had aspartame in it). I also experience anger, slow speech, and even more anxiety than usual when I have high phe levels, and this is noticeable in my job which includes a lot of discussions with colleagues and external people. These symptoms affect my work, my personal relationships, and my enjoyment of life negatively. Kuvan is routinely prescribed for adults in other countries so clearly health authorities in those countries recognise that Kuvan improves the medical outcomes and quality of life of patients, therefore I suggest that NICE has not taken into account the relevant evidence from those other countries, which include numerous studies that will not doubt have been cited by other respondents to this consultation.
For me as a person with PKU and one who has been on diet for life, Kuvan would be transformative if I responded to it. It would mean I could live a much freer and happier life, including not having to worry about my phe levels all the time and the symptoms of high levels, and so having more time to devote to work and family life, progressing my career and being more relaxed and happier as a friend, daughter, co-worker, and partner. It would mean being able to eat more natural protein and so being healthier in my body as well as my mind, knowing I was giving my body all the natural nutrients it needs especially going into middle age; being able to eat out and socialise more like everyone else, enjoying food more and being able to eat different foods, and being freer to travel and enjoying going to parts of the

world that would otherwise not be possible due to the difficulties of relying on all my prescriptions and a cuisine that had enough free foods for me to get by.
NICE has also ignored the fact that many adults with PKU simply cannot cope with dietary treatment. The NHS should not leave people without a realistic option for treatment. In particular, many adults who experience difficulties were told by the NHS when they were children in the 1970s-1990s that they did not need to continue the diet in their late teenage years and in adulthood, and so didn't. The NICE draft guidance does take into account that they were advised in this way, and that Kuvan would help them control their phenylalanine levels. Currently, the draft guidelines as a whole are unethical, for all the reasons stated above and below and more; to ignore the way these adult patients have been advised and treated in the past, and who have followed medical advice given to them that has impacted so negatively on their lives meaning they constantly struggle with high phe levels, would be especially unethical. Concomitantly, those like me who spend an enormous amount of time and energy at the expense of other areas of their lives on adhering to the diet because they always have done and need to keep it up should not be penalised by being restricted access to Kuvan or any other future treatments for PKU. NICE and the NHS should be prioritising funding for treatment to those of us who have health conditions that we have through no fault of our own, and which cannot be cured, unlike, for example, Type 2 Diabetes, which can be reversed through recourse to a diet, exercise, and healthy lifestyle.

NICE's Comments Regarding Women with PKU and Maternal PKU Syndrome; Pregnancy and Maternity Discrimination in NICE's Recommendations

NICE has not considered fully the harm of Maternal PKU Syndrome to the woman with PKU as well as to any unborn child. Worry about the potential of Maternal PKU Syndrome is significant for many women with PKU and lasts throughout the life period during which it is possible to get pregnant, from puberty until the menopause (childbearing years are not just 18-40, despite what NICE's draft guidance states on p. 25 at 3.24!). When deciding that Kuvan is not cost effective in adults, NICE has ignored the benefits to women with PKU of using Kuvan to help them have happy intimate relationships without having to worry about an unplanned pregnancy resulting in Maternal PKU Syndrome, and have safe and happy pregnancies, whether planned or not. This last point is significant, as no woman with PKU should have to go through life thinking she must only have a planned pregnancy or face the dire consequences for the unborn child and sense of personal guilt that comes with an unplanned PKU pregnancy. This worry is real and constant. It has affected my own life significantly. I grew up from the age of 12 being told about the negative consequences of Maternal PKU Syndrome by clinicians and it terrified me so much I have been unable to form healthy intimate relationships until well into my 30s. This was only when I realised - through the NSPKU's Survey Results (Ford S, O'Driscoll M, MacDonald A. Reproductive Experience of Women living with PKU; Molecular Genetics and Metabolism Reports
17 (2018) 64–68) - that I was not the only person that thought and felt this way, which I had always been extremely ashamed of and couldn't speak about, and thought that it was because something was psychologically wrong with me. Rather, this is of course an unsurprising reaction to being told from childhood that I could be responsible for a child having physical deformities and learning disabilities, and taking this heavy burden seriously and not receiving any clinical help in processing this. Having PKU as a woman has shaped my personal life beyond what most people could imagine and is directly responsible for the fact that I do not have children and may not ever have children. This is a source of deep distress to me; it has robbed me of years of happiness, and the NSPKU survey results and study show that I am far from alone in PKU having an extremely significant effect on my

sextual and reproductive health – both physical and mental. NICE should take these survey results and the article based on them extremely seriously and I am puzzled as to why it has not already done so – the voices of women PKU patients have already spoken in a large number through that and the draft guidance appears to have ignored them. By asking for more evidence, NICE is asking women with PKU to perform difficult and significant emotional labour disclosing details of their most intimate personal life and I expect NICE's subsequent documents relating to this consultation to acknowledge this explicitly and think carefully about what it is asking of people directly affected by PKU and, in the future, other conditions that relate to areas of psycho-sexual health and wellbeing and pregnancy.

I would also like to note that women without PKU don't have to think about Maternal PKU Syndrome if they happen to fall pregnant without planning it, so why should women with PKU have to endure this disadvantage? Women PKU patients should be able to access Kuvan throughout their lives not just during a pre-conception period and during pregnancy. To do otherwise would discriminate particularly egregiously against women with PKU in relation to pregnancy and maternity.

NICE has recognised that controlling phe levels is important in early pregnancy, ideally before conception, and has recognised that this would reduce the risks of Maternal PKU Syndrome. However, it has not considered in its proposal to stop treatment of Kuvan at 18 about how women would be able to cope with going onto the even stricter-than-usual pre-conception diet to avoid Maternal PKU Syndrome. I would suggest, as someone with 38 years-experience of the PKU diet, that most women who were treated with Kuvan from infancy would find the pre-conception diet more or less impossible, and NICE has not factored into its economic modelling the costs of the NHS treating more children born with Maternal PKU Syndrome as a result.

Furthermore, NICE has not included the harms from high levels in early pregnancy in the cost analysis. Nor has it taken into account the experiences of women with PKU who have gone through the pre-conception diet and a pregnancy. This is a time when hormonal changes and other health changes due to pregnancy make the diet extra difficult, and also a time which can result in severe illness that makes the diet extremely difficult both mentally and physically, potentially raising phe levels and also making the experience traumatic for the woman.

The hormonal changes experienced by women during the menopause should also be taken into account by NICE. Women need help through treatment with Kuvan to ensure they can maintain low phenylalanine levels throughout life and to help ensure they are as healthy as possible into old age. I believe that NICE has failed to take account of the issues experienced by women with PKU – whether they are at the stage in life where they want and can have child or not - and that this is a major failing in the draft guidance.

NICE's Proposals in Relation to People with Disabilities

People with learning disabilities are at a higher risk of being unable to control their phenylalanine levels with dietary treatment. The need for help with dietary treatment might also restrict the independence of people with learning difficulties. NICE recognised that people with learning difficulties might struggle with dietary treatment but there is no evidence that this has been included in the cost analysis.

NICE's Proposed Recommendation in Relation to Kuvan Dosage

NICE has recommended using KUVAN at a dose of 10mg/kg. I agree that clinicians in the UK will prescribe more efficiently than in the US and that an average dose of 10mg/kg is appropriate for the cost analysis. However, I believe that clinicians should be able to prescribe within the marketing authorisation, which ranges from 5mg/kg to 20mg/kg.

Conclusion

I believe that all people with PKU should have access to Kuvan on the NHS, and all future treatments for PKU that become available should also be funded to enable people with PKU to live full, happy lives, and fulfil their potential.

Name	
Comments on the ACD:	

As a 37 year old adult, born with PKU in 1983, I have had much experience of living with phenylketonuria (PKU). Due to the recent NICE decision to make Kuvan (Sapropterin) available to children under the age of 18, along with the many flaws the PKU community see in this decision, I will detail my experiences below which would show this treatment to be a harmful luxury for children living with the condition but vital for adults to live safe, healthy lives.

Childhood

My earliest memories as a small child with PKU were very healthy. My parents always had a healthy stock of prescribed low protein foods kept in the cupboard under the stairs, though they were extremely bland and basic, and my sister (2 years older and also born with PKU) and I were sharp and lively children. We lived in a street where there were many children our age and we were always outside doing everything that kids do; playing football, tennis, climbing trees etc. Other kids who knew us knew we couldn't eat like they did. They knew why we always had weird biscuits or couldn't accept food from them, but the kids who didn't know us often didn't understand. I was never shy and I handled questions from other kids very well, though my sister found this more difficult and grew more and more secretive about it as she got older.

I never really liked school, but I was a lively character and did mostly OK with my schoolwork throughout infants and junior school. At lunchtime I had school dinners, which the school dinner staff made separately from that of the other pupils, and I sat among my peers while eating a lunch which was entirely different to theirs. The food I ate in the dinner hall often looked weird, but my parents were organised and my diet was being maintained so my mentality was healthy and I easily dealt with any questions about my differences without any issues of cruelty or bullying. I was quick to stand up for myself against any peers in the school yard in the infants and junior school too. Life felt like it was all under control. I was a normal kid, but with a rare dietary need. That's how I saw it. I was confident, I had fun, I was mischievous and despite not being the model pupil I could keep up with my classwork when I got my head down. Not everything was perfect though.

Life was flowing perfectly and my parents were doing their part without fault, but there was already the foundations being laid in the background for things to go wrong. The NHS in the 1980's hadn't yet announced PKU dietary treatment to be a 'diet for life' as it is these days (and has been since the early 1990's), so my sister and I were told by medical professionals we would only be on treatment until the age of 8 (the age children were removed from treatment at that time). When my sister reached 8 years old they denied her removal from treatment and said she would need to stay on treatment until the age of 10. When she reached the age of 10 the goalposts were shifted again, this time to the age of 12. When my sister reached 12 professionals then announced to her the diet is required for life, but due to repeated broken promises and numerous disappointments my sister began

eating things she shouldn't have eaten. I was 2 years behind her, looking on as these years went by and learning my fate as her's was being altered repeatedly. We both began trying foods we shouldn't have been eating around this time. I quickly found my instinct to stand up for myself in the school yard had quickly withered away. My confidence was becoming extremely low and I had no idea this was happening due to the chocolate bars I had eaten on my way to school, the milk I drank on milk monitor duty and the consumption of anything else I might have been able to get my hands on while my parents continued to make me suitable low protein meals to keep me healthy.

Kids with PKU up until this point in time had been removed from PKU treatment by professionals, not as a choice, but as an instruction. My sister and I were later removed from the diet as a result of not following it strictly enough, though they didn't stop to consider the unstable/unreliable information we'd been given in the years leading up to our rebellion. We were only children. And we had only just reached an age where we had a little freedom to visit shops without parents and to walk to school without being walked by an elder when I began to eat the wrong things at 11 years old.

LIKE MANY PKU ADULTS BEFORE US, WE WERE REMOVED FROM TREATMENT (BY THE NHS) AS CHILDREN.

WE NEEDED SUPPORT, NOT DISMISSAL!!!

I started secondary school later that year, before the point I was dismissed from treatment, and just couldn't put my finger on why I was in such cognitive decline. I couldn't explain it to anyone because I didn't understand it myself and my self expression was suffering as a result of it all too. I took an exam in my first week of secondary school to determine what sets I would be in when I reached the classrooms and I wasn't fazed by the test at all. I always felt I was as capable as my peers in primary school, but I didn't do half as well as my pals. I just didn't understand how I could have done so badly in comparison. I remember the tears while explaining my results to my parents the day I learned how I'd done, but I was in the right sets for my level of intelligence while not properly adhering to the strict PKU diet - the lower sets. The secondary school I went to was known to be one of the rougher schools in the city and the confidence I once had really would have done me a huge favour many, many times in and out of school between 11-16 years. I had memories of being able to deal with situations, but found myself unexplainably easy to intimidate. It wasn't the physicality I found intimidating, it was the psychological battle of confrontation. I just wasn't quick enough upstairs to deal with it and I was immediately overwhelmed (unlike when I was on treatment in primary school). I wasn't big in my secondary school days, but I wasn't the smallest either and I'd even find myself intimidated when confronted by people smaller than myself who I knew I shouldn't have been intimidated by. These were all minor occasions though and I was never bullied (thank God). I had a large group of friends and I was in amongst the cooler crowd. Not that I was cool myself. Not a chance! But I had a sense of humour and I think that's what saved the day for me in those days. When I was walking home from school, and various other times, I'd miss what was being said in the crowd I was in and I'd always humiliate myself with my inability to keep up with what's going on by losing focus of the conversation/banter. If there was an award for the person who'd been told they were 'slow' I'd have won it a million times over. I found it difficult to respond to 'banter' which was at my expense but it came at me often and I eventually learned to make fun of myself, so I began to make jokes aimed at myself to outdo any unfair 'banter'. I used humour as a defence mechanism and it worked for me, but I

wouldn't aim it at anyone other than myself because that would lead to my humiliation more often than not. I only ever stuck up for myself when I was cornered and my back was against the wall, but at least I had that in me. I needed to go through turmoil before that point though. Every day was difficult. I wasn't great in any of my lessons either. I was very daydreamy, especially after dinner - which was either pizza and chips, or sausage and chips, or burger and chips (none of which is suitable for me). It was during these times that the NHS dismissed me from treatment, but they didn't ask how I was feeling and I had no idea my decline was down to my consumption of high protein foods. I left school with 1 GCSE and went straight into the workplace rather than college, because academia was such a hard slog and I was living in a clouded mind which I couldn't make sense of and couldn't explain to anybody - not even my sister who was experiencing the same thing. Neither of us understood our experiences because we were never informed about what symptoms to be aware of by anyone who had experienced it before. We didn't realise phenylketonuria was hurting us and we had been promised to come off diet as younger children before being removed by professionals in the early days of secondary school, so we didn't consider it as a dangerous thing to be off treatment as medical professionals instructed kids to come off treatment and were easily willing to remove kids who were beginning to find difficulty with the lifestyle. Baring in mind, that lifestyle was (and is now) the daily protein equivalent of 2 slices of bread. That strict! And the dietary team in the clinic washed their hands of me at 13 years old and my sister at 15 because we needed the support they were unwilling to give. We were let down then, just like we are again now as adults while we continue to campaign unsuccessfully for a drug which has been on the market for 12 long years. So the very adults being left without modern treatments are the exact people who were let down by the system as children and the struggles they suffered as the years went on were NOT their fault because they were wrongly advised by professionals. I'm just getting started!

Adulthood

My first real job after school was working as a sign maker, which I went into at 17 years old. My concentration levels and my mindset were both very poor, though, luckily, my morale was high. My manager first put me on the computer to design the sign graphics, but I proved to be a failure in that role because my mind struggled to digest the instructions given to me and my efforts were often poor. I always felt like I needed help from one of the other guys who worked in the unit. I always felt hopeless and while I was trying my hardest I was always in a state of internal distress caused by my knowing that I wasn't good enough and to ask for help was humiliating. I was then shifted over to work on the assembly of the signs instead, but even though I was capable my manager could never see my capability because I was a walking bag of nerves and I always felt the weight of an entire world of pressure on me in that place - meaning I'd often make stupid mistakes. I knew I'd failed to gain my manager's respect and I just couldn't do anything to help it. I got along very well with the other guys in that job, but the manager just didn't take to me at all due to my unstable and unreliable ways and I felt his mistrust and lack of respect with every fibre of my being. The guys in the unit jokingly nicknamed me 'Knackers' because I reminded one of them of a guy he once knew with that nickname who had tourettes and so it became my name too. I was always able to handle jokes and always able to have fun with people who didn't judge. Despite my experiences in that workplace being mostly unsuccessful I have remained in touch with 3 of all 4 of those guys, one of them becoming my best friend for almost 20 years before he was killed in an accident last year - which shows the qualities I had in my personality despite my failure in my job. Had I been

on treatment I would have performed better and I know this now, but did not back then.
I left that job after 2 years and went into a job at [redacted], working in an office role at a car parts warehouse. This was the most embarrassing and upsetting work experience I have ever had. My mother helped get me into this job, as she was well respected in the company as the P.A. for the company director and she spoke very highly of the lady who was to become my manager. My mother was so good at her job and the lady who took me on would probably have expected me to be cut from a similar cloth, but I couldn't grasp any of my duties at all. When I was filing I'd take forever and make mistakes. When I was using the computing system I would glaze over and lose concentration. The blokes around me never said anything directly to me to put me down, but I knew my place. My personality didn't save me in that place. I didn't fit in at all and my phenylalanine fuelled mind made a mockery of me with every task I took on. I would have to go into the warehouse and find a car part, but I would often come back to one of the guys telling them I couldn't find it so they would come with me and they would find it instantly. I knew when they found the part they would think I was an absolute tool. I soon got pulled into the manager's office. Not the lady my mother knew. The manager of the full place. He pointed out my imperfections and how they were causing my performance to be substandard, or even below substandard, looking to get a response. I could tell that guy didn't think anything of me. I knew by the way he looked at me with his piercing eyes. He didn't think much of me at all. At this point I tried getting back on treatment, hoping that would improve things after my sister had returned to treatment due to pregnancy, but my protein levels came crashing down too fast due to my determination and I felt dizzy. My concentration was even worse. I couldn't get my diet under any control and I lost that job. They were going to sack me so I resigned. The humiliation of being such a failure in the work environment my mother had placed me in to work with friends who held her in high regard was a real tough one to take. I would have felt humiliated by that experience even if my mother hadn't been involved, but to think my absent mindedness and clouded brain had lost her any respect from her colleagues made things a million times worse. At this point my confidence was extremely low.

I worked in a tile showroom for 2 years after that and had a good experience there, starting at 20 years old, and the people I was surrounded by created a much more welcoming atmosphere. I felt the job role didn't put as much pressure on me and I always felt respected in a way I had never been in any job beforehand. It was a customer facing role and, although my mind wasn't at it's best, I was a happy go lucky character and had tons of empathy which always went down well with customers. The empathy obviously came from 10 years of mental suffering and the consequences of people's reactions to my lack of focus and inability to perform in many, many ways (in some social crowds and in many work scenarios). I left that tile showroom to become a tiler and despite having the opposite demeanour of the usual 'Jack the Lad' construction worker I was good at that job. I was doubted by a customer once due to being quiet, under-confident and young, but she was on my side when she started to see how her kitchen was turning out. Drawing straight lines on a wall/floor and sticking tiles didn't need the same levels of concentration and I didn't have to deal with people, so I was comfortable and I had good reason to be proud of my work in those days before the work began to dry up in a self employed spell leading to a job in a call centre.

I had a horrendous start to that call centre job and another manager who didn't take to me. This guy mocked me and apparently asked another worker in the place to get me sacked on the basis of not being up to the job, which the guy refused as he could see I was putting the effort in. I was hanging onto that position by the skin

of my teeth. All of this was going on while I was making some good friends in the office. I was very well liked from day one. I always had a smile and a joke to tell, despite being scatty and quite nervous, and I felt almost the whole office warmed to me - other than the odd one or two who felt they were above my sensitive and under confident demeanour to the extent of showing disrespect. I successfully returned to treatment while working in this place and my performance rocketed to 'core performer' on my development plan. I was given the chance to try stand up comedy as part of a work charity event, so I did. I was a bag of nerves, but jokes were my thing and despite screwing it up with stage fright at first I did a great job in front of over 100 people. There was NO WAY I'd have been able to do this before getting back on treatment. I did more comedy at charity events and in comedy clubs and I always got laughs, but I would always forget my lines at some point (which I put down to PKU damage).

I began to believe in myself and took on some ambitious goals, but despite achieving my goals I can't shake off the constant feeling of people's doubts. All of those scenarios, SOME of them mentioned above, have taken their toll on me in such a way that I still read people's expressions and if someone gives me the impression that they doubt me, fail to respect how I am, or use a tone that suggests passive aggression or toxicity then I quickly become uncomfortable in that environment. So despite my performance being better at work these days I consider myself as a person with anxiety, partly due to the experiences I've suffered while being off treatment (especially in the workplace as an ADULT), and also partly due to the possible damage to my brain caused by the 18 years of non adherence to the recommended lifestyle since being removed from treatment by medical professionals despite my parent's pleads for their support at the time which clinicians and consultants brushed aside and left myself and my sister to struggle all of these years.

Relationships

When I was 18 I met my ex-girlfriend. She was absolutely beautiful and I was smitten, but I was also at the age where I wasn't following today's recommended lifestyle for people suffering with PKU and I was going through lots of trauma in many ways (as above). My confidence was consistently taking huge hits and my mental clarity was always severely affected by an awful brain fog and an inability to express myself. My personal boundaries were something I didn't understand about myself and if I couldn't tell my partner what is important to me, then what kind of foundation is that relationship going to be built on? After the first year of being together (of almost 8) things were beginning to turn sour, but I wanted us to stay together. I felt I was VERY lucky to have her and I didn't believe I would get anyone as nice if I let her go. I tried really hard to make things work, but the longer the relationship went on the more toxic it grew. She stopped me from seeing friends, battled with me if I went on a night out, didn't mix with my family (who were always kind) and had me trapped in a life cycle of 'work, tea, bed' in the period we lived together. She obviously knew I didn't express myself greatly and could obviously sense emotional and cognitive vulnerabilities I was carrying and used my weaknesses to manipulate me into a lifestyle she wanted for me. The relationship grew colder and colder and became completely loveless. In the final few years of being together I hated my life, but felt I couldn't escape from it. I felt I wasn't worth anything else and couldn't visualise anything positive coming from moving on and being single, so I stayed with her and suffered more. I continued to try to make it work and do things that would hopefully help some warmth back into the relationship until the age of 26, when I broke down in tears to my mother about it all and began to ready myself to move back home and get my life back together

again. It took a couple of weeks and some kind words from girls I worked with at the time to build up my sense of self worth before I was able to break it off, but I did it! So while I was going through all of that turmoil in many workplaces I was going through worse in my private life while my emotional state and vulnerable expression was being manipulated and further damaged every single day. I have met many people with PKU and the majority have revealed experiences of manipulative/abusive relationships.

As a result of everything mentioned above, children these days know that PKU is a condition for life. We didn't!

They are not instructed to come off treatment by professionals like we were, meaning children won't suffer the broken promises we suffered. They have more stability!

Parents will have a better chance to maintain their children's diets and teach them the fundamentals of living with PKU into their teenage years ready for adulthood. We were let down before that point!

Children with PKU have a much more solid foundation these days than our generation ever did when we were of that age, but there are many, many adults suffering! (because they had treatment denied to them in their childhood and now it's happening again)

Giving treatments to children with PKU, then taking it away at the age they reach the working world would be absolutely disastrous.

Adults with PKU need access to modern treatments such as Kuvan and they need it now!

Name	
Comments on the ACD:	

Dear Appraisal Committee,

I had the opportunity to read the appraisal consultation document for sapropterin for treating phenylketonuria, and I was deeply disappointed and disturbed by the recommendations given by the committee.

What struck me as deeply ignorant at best and malicious at worst was the statement "The dose of sapropterin is based on weight so costs are higher for adults than children but there is no extra increase in the quality of life for adults".

At the age of 18, I had no understanding of how to manage/micro-manage the PKU diet. At the age of 18, I also had A, B, C grades in A Levels, B, C grades in AS Levels, and 3 A's, 5 B's and 2'Cs in GCSE with two Certificate of Merit awards for ICT and Business & Communication for outstanding effort and managed to get into University [redacted].

Due to my lack of understanding of the diet and the ongoing burden of micro-managing the diet alongside with university studies, I ended up failing and retaking

my first year, and effectively getting a third in my 2nd year due to being so distracted and foggy minded with all the work. When I received my 2nd year results I fell into a deep state of uncontrollable anxiety depression. It got so bad that I had to be prescribed Propranolol (to reduce the anxiety – I didn't feel positive about my outcome, but this was enough to get me revising again) and Domperidone, to stop me from vomiting any food that entered my body due to the heightened anxiety I had at the time. At this point I became a shell of myself and became far more withdrawn from my friends and university colleagues.

Eventually I did well enough to get a 2:2 BSc Computer Science w/ honours but even to this day I wonder how things would have been had I been able to effectively manage my diet if I had learned how to control the diet earlier, or even better yet, had more flexibility with Sapropterin so I could have managed both the diet and my private life. Giving patients the sapropterin drug from the age up to 18 and then taking it away from them when they most need to be in control of their lives is cruel and barbaric, and only serves to hamper the possibilities in their future when they need the most support.

One could argue that micro-managing the diet is a good enough solution compared to sapropterin. I can tell you that I have consistently struggled to get my diet in order, with my levels continuously spiking. Here are my phe levels for the past two years:

Date	Phe (umol/L)	Date	Phe (umol/L)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		

In case my anecdotal evidence doesn't convince you, I hope raw data convinces you. From December 13th 2019 I was starting to get my diet back together until between 27th April 2020 and September 26th 2020 I was having very little luck managing the diet. The causes of the spikes were accidentally measuring the wrong amount due to weighing scales running low on battery and thus scales reading the wrong results.

Another reason was forgetting extra supplements due to the change in environment (COVID meant working from home) meaning that I lost my "memory prompts" (at 7am at home, I'd have a supplement, at 12pm at work I'd have another, and before I'd leave work, I'd have my final supplement) and would often forget to take supplements due to my old routine being shaken up.

One more reason was after some number crunching, it turns out I needed another supplement – this was only spotted when my numbers didn't go down. Unfortunately, at that point my mood would be of frustration and aggression from

the high phe as it was *another* thing to manage in the diet. I eventually persevered and my phe levels are lower and I'm back to my old self.

Not getting my phe levels has and is hampering many aspects of my life; I no longer go out to see my friends as the occasion is always social eating, which I struggle to participate in. I've even had to avoid seeing family on their birthdays because of not wanting to sit in a restaurant and eat a lettuce or cucumber slices while other family members eat a full meal.

Office work responsibilities that were once child's play become a struggle, which leads to tense relationships between yourself and higher management because PKU isn't visible and the same people can't tell if you're intentionally being stupid, trying to slack off, or if someone has kidnapped the real you and replaced you with an imposter.

Then again, you already know this as you wrote it in your appraisal – point 3.5, which directly contradicts your statement of "no extra increase in the quality of life for adults".

The recommendations also hinted that there was an issue of cost. In 3.11 of the appraisal recommendations, you mention "Clinical experts highlighted that some people with PKU who take sapropterin can completely remove protein substitutes from their diet, referencing a forthcoming systematic review." This is something I highly concur with. As of now these are the things on my prescription:

- Fate Low Protein All Purpose Mix (flour substitute)
- Loprofin Low Protein Pasta Long Cut Spaghetti (spaghetti substitute)
- Mevalia Low Protein Spaghetti (spaghetti substitute)
- PKU Sphere 20 (protein supplement)
- Promin Plus Low Protein Pasta Spirals (pasta spirals substitute)
- ProZero liquid (milk substitute)

If Sapropterin was to increase my intake of 6g to 10g, I can easily cut out the milk. Up to 15g, I can seriously consider cutting out all the pasta substitutes – or at least reducing the amount I order on prescription. I can't imagine all of those ingredients on prescription are cheap. Not only that, speaking as someone who has to eat these foods – they aren't particularly nice to consume.

It's something one has to put up with as part of the diet, but they generally feel lesser than their counterparts – the most egregious example is the Low Protein Rice. When I wasn't controlling my diet properly, I had a chance to taste rice and it's such a tasty staple of the diet. The low protein alternative tastes like oily pellets in comparison and lack the real rice's ability to soak up flavours from ingredients around it, leaving a film of taste on the outside.

This isn't the only example, and as someone who has been off diet, I have always and always will appreciate the companies trying to make low protein substitutes of my favourite food, but it can never compare to the real deal.

Then there is the fact that one has to continuously make this stuff. I am greatly fortunate I have parents who enjoys cooking immensely and derive happiness out me enjoying the tasty food they cook, but I can't imagine others are as lucky as me to have essentially "staff members" on standby dedicated to cooking me low protein food.

This is a privilege that I have that many others do not have and it's absurd that NICE wouldn't want to go out of their way to alleviate the burden not only on PKU patients, but the people surrounding them like their family members, their loved ones, and/or their carers as you pointed out in 3.6.

With sapropterin, NICE could look into improving the lives of not just people with PKU, but the people around them. PKU isn't just a burden on the person with PKU, it's a burden on the people around the people who have PKU who have responsibilities to ensure the person with PKU doesn't end up with high phenylalanine. It impacts their mental health, social abilities, and wellbeing.

I really do hope you strongly reconsider your approach and recommend Sapropterin for all ages.

I'd like to add a bit more to my response as a bit of an update given the events that have transpired in the 15 days since my last email.

I recently found my phe levels have risen to 760umol/L. I strongly suspect this is because the weighing scales battery is dead, but I ultimately no idea what was the real reason. Given how I'm on 6g of protein per day, any slight increase can mess around with the results. I've been noticing I've been a lot more short tempered before the results, and it's still ongoing as I'm having to continuously make sure my levels are low meanwhile taking on responsibilities as an adult.

Sadly that's not even the worst news I've had. You see, my short temperedness has also been a result of me trying to contact my pharmacy and my GP to understand why my usual spaghetti on prescription hasn't came through - I filled this prescription in on the 3rd March and only recently discovered that it didn't come through from the pharmacy as life got in the way. Tracking it down, the pharmacy insisted they got no prescriptions from my doctor and my doctor insisted they sent the prescription on the 10th.

After many phone calls later and lots of panicked emails to my dietitian I eventually found out the true culprit was the GP, as they filled in the data but did not manage to get the doctor's approval. I found this out ***yesterday***. And now the GP has done their bit, I have to sit and wait and hope there are zero delays from my pharmacist. Meanwhile, I'm low on low phe prescription foods and have to resort to finding old low protein food from the past (some that may even be out of date, unused because of how I didn't enjoy them at the time) and use that like the previously mentioned low protein rice, or fruits and vegetables.

The PKU diet isn't a valid alternative for any PKU patients if there are alternatives available. The risk of failng the diet and failing my mental health and wellbeing as a result is too high.

Name	
Role	
Comments on the ACD: The decision to make Sapropterin available for children for PKU is a welcome development. However I would question the decision to limit the dose to 10mg/kg. Weight appears to have been given to the opinion of one clinician as stated on p15	

stating that little difference in outcome was noted with increase in dose from 10mg/kg to 20mg/kg. Muntau et al (2017) showed that in a phase IIIb trial only 2 of 27 had dosage increased to 20mg/kg. This was deemed necessary to achieve Phenylalanine (Phe) tolerance >20% above baseline. I would suggest that by limiting the dosage 7% of children who would have a clinically significant response would be denied sapropterin treatment with all the benefits conferred. In addition to benefits on terms of brain development, there are further benefits to be gained from a more balanced diet with less fat and carbohydrate, increased natural protein and reduced amount of protein substitute often containing high amounts of sugar to ensure palatability. Indeed there is much anecdotal evidence in the PKU community of children having cavity fillings and tooth removal. This is confirmed in published evidence (Singh-Hugsen et al, 2016) that children with PKU had a high decayed, missing and filled surfaces index as compared to diabetic and healthy control children, which means they had higher caries rates. The committee state on P16 that there is little evidence to estimate quality of life in children with PKU. There is a specific PKU quality of life questionnaire (PKU-QOL) and there is a version for children. Alptekin et al (2018) used this questionnaire in a study including 20 children aged 9-11 years and 22 children aged 12- 15 years. This study showed that PKU affected QOL of children and younger people the most compared to adults, especially in terms of social and overall impact. Of note there was no control group included and a minority of children studied were taking sapropterin.
I would request the decision to stop sapropterin (Kuvan) at age 18 years be reviewed, request continuation of therapy beyond the age of 18 years, and would request the following are considered in making a final decision.

I am concerned that the full benefits of optimum Phenyalanine levels (Phe) and hence the benefits of kuvan, have not been fully considered. On page 3 the aim of treatment is stated as reduction of Phenylalanine levels and less restricted diet, and subsequent impact on brain damage. However I would like to draw attention to the fact that raised Phenylalanine has wider impact than brain development. I would draw attention to a paper by Trefz et al (2019) which reported adults with PKU as compared to age matched controls has higher rates of depression, ischaemic heart disease, asthma, COPD, dizziness/ giddiness, diabetes mellitus, gastroenteritis/colitis, stress and adjustment disorders and acquired limb deformities. The increased healthcare burden was also reflected in higher rates of prescription medication to manage these conditions. Of note only <1.3% were receiving sapropterin and 13.8% dietary amino acid supplement. None the less this highlights additional costs of poorly controlled PKU and further potential benefit for kuvan in adults with PKU. A review article by Vardy et al (2020) on PKU, co-morbidity and ageing also outlines some of the potential mechanisms and the evidence to date for wider impact on health of the adult with PKU. A further contribution to overall health is the constraints of a restricted diet on exercise. It is difficult to achieve satiety on a low protein diet which means many adults report high levels of fatigue before and after exercise. Hence achieving a healthy lifestyle is limited and this may at least in part account for the higher rates of comorbidity reported such as diabetes mellitus and ischaemic heart disease.

P4 states there is no additional Quality of life (QoL) impact in adults to offset additional costs. I would again would draw attention to the development of a specific quality of life questionnaire (PKU-QOL) more sensitive to the issues that affect people with PKU, developed by Regnault et al (2015). This has been used in a paper in 2020 by Barta et al which studied 88 adults with age interquartile range of 25-40 years. Those with suboptimal dietary adherence, defined by blood

Phe levels of 753 ± 137 µmol/l in the last 10 years, had poorer quality of life scores on the PKU-QOL, compared to these with mean Phe <600 in last 10 years.

P4 states there is no risk of irreversible brain damage in adults, and on p5 states this to be reversible. This implies there to be no on-going brain generation after the age of 18 years. I would dispute this based on evidence from studies relating to dementia, which provide helpful insights into the ageing brain. The concept of adult hippocampal neurogenesis, the ability of the memory centre of the brain to produce new nerve cells throughout life, was hypothesized by Errikson in 1998. In 2019 Moreno-Jimenez at el described evidence of this process in the human brain, demonstrating persistence of this process during physiological ageing until the 9th decade of life. In vivo evidence for this is available from brain imaging studies in PKU using PET including 16 participants age 16-47 years had reduced tyrosine influx and reduced protein synthesis (a process important for memory) in relation to higher Phe levels.

Furthermore I am concerned that stopping Kuvan at the age of 18 will result in significant numbers of adults with PKU discontinuing diet. Transition of people with PKU to adult services is challenging, with loss of longstanding support from both paediatric services and family, in move towards independence and self-management. This transition period is already known to represents the highest risk time for reduced compliance and becoming lost to treatment, for people with PKU. Ceasing access to a treatment that has assisted with the daily management, including liberalising the diet, seems very likely to add another challenge to a challenging transition. Returning to diet after a period of relaxation is extremely difficult. The evidence indeed confirms this showing that in those where diet is discontinued it is unlikely to be maintained with a study by Bik et al (2008) showing that of 53 adults with PKU returning to diet only 10 managed to maintain this at 9 months. Gassio et al (2003) also showed that of 15 adults with PKU (either resuming diet or late diagnosed) only 47% managed to attain regular to good dietary control.

3. I would request the decision not to provide Kuvan for women with PKU in the context of preconception and pregnancy be reviewed and amended for the following reasons.

P4 states there to be insufficient evidence to show how sapropterin may reduce harm to the unborn child in women with PKU who are pregnant of trying to conceive. However we do know that raised Phenylalanine causes harm to the unborn child. Without very strict dietary management in the pre and post conception stages their babies are at very high risk of mental retardation, microcephaly, congenital heart disease and intrauterine growth retardation (Levy and Ghavarni 1996). We also know as per the appraisal document that approximately half of pregnancies are unplanned, of note this rate is similar to the general population (45%, https://www.gov.uk/government/publications/health-matters-reproductive-health-and-pregnancy-planning/health-matters-reproductive-health-and-pregnancy-planning). Hence the benefit of sapropterin on Phe levels would in turn reduce risk of harm in the scenario of unplanned pregnancy. The conclusion reached appears disparate to the statement on p7 that ‘
the committee concluded that high blood Phe levels in pregnancy can have harmful effects on the unborn child. Early control of Phe levels, ideally before conception, would reduce the risks. ‘

P6 states that there are no strict clinical guidelines or target Phe levels for pregnant women with PKU. This is contrary to guidance in the European consensus guidelines (Wegberg et al, 2017) which states that 'Women need to be advised at each clinic that dietary treatment or BH4 therapy (sapropterin) (or both) is essential pre-conception and during pregnancy.' The NHS Clinical commissioning policy published in 2013 (https://www.england.nhs.uk/wp-content/uploads/2013/04/e12-p-a.pdf) states that 'Very strict dietary control and the maintenance of plasma Phe levels between 100 and 300 µmol/L throughout pregnancy can prevent birth and developmental defects. Outcomes are good if women are commenced on a pre- conception diet and Phe levels are within the former range when they conceive or if the target range can be achieved within eight weeks after conception. Therefore we need to use all the tools available to us, including sapropterin, to try and obtain metabolic control in these women for the duration of pregnancy.' The current guidance suggest that women off diet can simply return to diet but does not take into account the inherent difficulty that is involved, issues described well in the Ford et al paper from 2018. On P7 it is stated that outcomes for maternal PKU are better than US. Of note in the US medicinal foods are not available on health insurance, hence we would anticipate the outcome to be better in the UK. However I would expect it to be better than at present with the benefit of Kuvan.

P25, requests further evidence of effectiveness of kuvan in women of child bearing age planning to conceive or who are pregnant:
MRC guidance 1993 (Cockburn et al) states that:
-Very tight control of Phe levels is necessary pre conception and during pregnancy of between 60-250micromol/l
-That termination should be offered to those with pre-conception Phe of >900 and considered in those where levels >700.
-Due to the positive amino acid gradient across the placenta the fetus is exposed to even higher Phenylalanine concentrations than the mother. Biochemical monitoring should be undertaken
-Pregnancy should be closely monitored due to risk of harm to the unborn child
I would request the committee further consider the excess burden placed on women under the current policy, of an expectation to be able to make significant dietary adjustment at a time where pregnancy itself may result in symptoms which make certain foods difficult to eat.

Should the committee reconsider the decision affecting provision of sapropterin for pre-conception and pregnancy I would also request consideration of provision post-partum. The rational being that the lived experience of women with PKU during pregnancy is that protein tolerance increases naturally throughout pregnancy as the growing baby uses protein for growth. In practice this means that in the later trimesters of pregnancy the mother has a relatively liberalised diet compared to the preconception phase when the diet is severely restricted. It is therefore perhaps unsurprising that most mothers with PKU report extreme difficulty in returning to their pre pregnancy diet in the immediate period following the birth of the child. They find needing to manage a restrictive diet while also adjusting to the challenges of a new baby virtually impossible and that then high Phe levels expose them to higher risks of post-natal depression, anxiety and poorer executive function for an extended period after the birth of the child. For this reason, I suggest that any consideration consider on-going access for at least six months post birth to provide the mother with an opportunity to adjust to motherhood before needing to return to a restrictive, time consuming dietary therapy.

4. Some of the comments by the committee relate to lack of evidence. For example: P16; Long-term brain damage in children is an important aspect of PKU, but there is little evidence to estimate its effect on quality of life
P22 The committee concluded that the costs of long-term brain damage after uncontrolled Phe levels in childhood, and damage to the unborn child in maternal PKU syndrome, may be substantial. However, these costs are unknown and are not appropriate to include in a model with a 1-year time horizon.
It would be helpful to the clinical and academic community for the committee to outline the research priorities, that are feasible to complete and avoid unnecessary harm resulting from raised Phe levels, that would aid the committee in making future recommendations.

5. I have concerns around equity of impact of kuvan on certain groups.
P26, in relation to equalities states that further evidence would be welcome.
The UK maternal PKU registry published by Lee et a states that:
'Neonatal birth weight and head circumference are greater, the incidence of congenital heart disease is lower, and developmental and intelligence quotients are higher at 4 and 8 years of age in those offspring whose mothers went on the diet before they were born.' Outcomes were better in those on diet preconception compared to post conception, that is with better controlled Phe levels. The evidence shows that in those where diet is discontinued it is unlikely to be maintained with a study by Bik et al (2008) showing that of 53 adults with PKU returning to diet only 10 managed to maintain this at 9 months. Gassio et al (2003) also showed that of 15 adults with PKU (either resuming diet or late diagnosed) only 47% managed to attain regular to good dietary control. Hence it is more likely than not that control of Phe will be lost after discontinuation of sapropterin at age 18 years will disproportionately impact women given the implications for pregnancy.

6. I would request the review date of the policy be reviewed and reduced from 3 years, referred to on P28, to 2 years. The rationale is that Public Health England is at present collating a registry of those with PKU in the UK, currently with 2000 people on this register. It is anticipated that data which may answer some of the further questions posed by this appraisal would be possible in 2 years, particularly should the committee specify the research priorities that would aid decision making in relation to a policy in sapropterin.

Name	
Comments on the ACD:	
We agree with the recommendation that Sapropterin will be offered to children with phenylketonuria that respond to the medication. This will undoubtedly lead to improved phenylalanine levels and contribute to improved outcomes in these patients from a clinical perspective. The benefits of a less restrictive diet will extend to a psychosocial perspective. We are very concerned that the recommendation is that beyond 18 years of age Sapropterin will be discontinued. It appears this decision has been made on the assumptions that : i) Maintaining blood phenylalanine concentrations of 120 to 600µmol/L by the alternative treatment of an extremely restrictive low protein diet is achievable. Evidence suggests that this diet is not possible in 43%of adult patients (Ford et al 2018) and in the UK and Australia, 80% of	

adult patients with phenylketonuria do not achieve blood phenylalanine levels of below 600µmol/L (Walter et al. 2002).

ii) After the age of 18 years the consequence of high blood phenylalanine concentrations is not of concern. The European guidelines (van Wedberg et al 2017) Statement #8 – Treatment for life is recommended for every patient with PKU. Significant sub optimal outcomes exist in adults with early treated phenylketonuria including executive function deficits, attention problems, decreased verbal memory, expressive naming and verbal fluency as well as social and emotional difficulties (Van Wedberg et al 2017).

It is known that high phenylalanine levels cause reduced executive function, concentration, fatigue ability to form relationships and increased levels of anxiety and depression in Adults. Stopping Sapropterin at 18 would mean a person with phenylketonuria would have to make significant reductions in natural protein only achieved with severely restrictive diets supported by additional protein substitutes and low protein foods. A change that would be extremely difficult to manage at a tender age when significant life changes are approaching including entering professional employment, apprenticeships, university, leaving parent's home. These are times when mental health is known to be at significant risk.

We strongly recommend Sapropterin should be available throughout life to people with phenylketonuria that respond.

We have serious concerns Sapropterin is not being recommended as first line use in females with phenylketonuria planning pregnancy. We recommend Sapropterin is made available to females with phenylketonuria as first line use during pre conception and during pregnancy and breast feeding.

It is well known that high blood phenylalanine concentrations are tetragenic. Maternal PKU syndrome can cause microcephaly, mental retardation, cardiac defects, spontaneous abortion and low birth weight (Van Wedberg et al 2017).

The burden of a low protein diet during pregnancy is extremely high. The diet is required to be restricted even further to significantly reduce blood phenylalnine concentrations to 120-360umol/l (van Wedberg et al 2017). If pregnancy is difficult and is complicated by illness such as morning sickness or gastrooesophagel reflux or gestational diabetes maintaining these strict phenylalnine blood concentrations can become close to impossible. Inadequate calorie intake secondary to nausea and vomiting is often contributory to catabolism causing dangerously high phenylalnine levels.

The consequential costs of a baby born with maternal phenylketonuria syndrome are difficult to calculate but must surely be much higher than the cost of using Saproterin as first line medication through pregnancy.

Post partum blood phenylalanine concentrations are likely to rise and consequentially make the first stages of motherhood more difficult. Sapropterin would likely improve the baby's care and help manage mental health of the mother post partum

Using Sapropterin only as a second line treatment is an unnecessary delay, during which time damage may be happening in Utero.

4. Micronutrient deficiencies secondary to a severely restricted diet

Inadequate intake of micronutrients including vitamin B12, iron, zinc, vitamin D3, calcium, selenium, iodine and long-chain polyunsaturated fatty acids are common in people with Phenylketonuria (Hochuli et al 2017; Rhode et al. 2013; Infante et al 2001; Moseley et al 2002). Sapropterin and a consequentially relaxed diet may contribute to the consumption of foods higher in these micronutrients and therefore reduce the likelihood of deficiencies and their consequences in Adults if Sapropterin was available. Conversely a change in dietary restrictions at 18 years old would likely be only partially achievable with a likely inadequate intake of amino acid substitute, therefore increasing risk of micronutrient deficiencies.

5. We are concerned that the cost/benefit analysis has not taken into consideration the anticipation that stopping Sapropterin at 18 years will lead to

1. Increased phenylalnine levels when a severely restrictive diet is commenced with high potential for inability to achieve required restrictions. This has the potential to contribute to increased anxiety levels and depression and consequentially the need for additional services such as psychology and counselling.
2. The consequences of a severely restricted diet in adult life can include vitamin and mineral deficiency. The cost implications of this could be significant. For example, in regards to calcium and the increased risk of osteoporosis and fractures.

The knowledge of long term health consequences for people with early treated phenylketonuria as they reach older ages are not yet fully understood. Sapropterin has the potential to reduce the impact of these yet unknown consequences.

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eference

Name	
Comments on the ACD:	
As the grandmother of a young lady with PKU who has managed her condition well, with considerable help from her mother, I would like to make this observation. Being on a very restricted diet for life is no fun. While at home with parents and siblings who can help to shop, cook, and collect prescribed foods from a pharmacy (which in it's self is often very difficult) life can be quite bearable. Once living away from home at Uni or for work, where family help is not readily available life becomes quite different and the diet becomes time consuming. Many youngsters do not like to be different from their peers, so may not adhere very strictly to the diet, leading to well documented ill health. Once Kuvan has been prescribed for a boy or girl, changing from a quite relaxed diet to a very strict one at the age of 18 years could cause lots of problems, as this is the time young people may go to University, or leave home for work. If a young lady wishes to have a baby, the diet must be very strictly followed, putting stress on someone who should be happy and relaxed. Imagine if she was able to have Kuvan, just how much more she could enjoy her pregnancy. Most people are over the age of 18 years old when they wish for a baby, so stopping Kuvan at that age is cruel.	

Name	Rt Hon Jeremy Hunt MP
Comments on the ACD:	
I am writing regarding your recently issued guidance on the use of sapropterin for children with rare inherited metabolic condition phenylketonuria (PKU). Having met a number of families affected by PKU I am delighted that you have decided to recommend sapropterin for use in children. However, I would urge you to go further and recommend its use in adults too. Your guidance admits that brain damage and other mental health issues can affect patients with PKU after the age of 18 and that brains continue to develop up until the age of 25. As such it is perplexing that you have not recommended the treatment for adults. It will be incredibly difficult for those turning 18 to suddenly	

face having to stop taking this life changing medicine. The overwhelming response from people that live with the disease and dietary treatment is that this will be harmful to young people just as they start to move to an independent life. The damage this may cause to their mental as well as physical well-being does not appear to have been considered in your guidance and so I would urge you to do so.

I understand the concerns set out in the guidance regarding the evidence however I would ask you to approach this appraisal with realistic assumptions about the evidence base. PKU is a rare condition affecting the brain which may be less studied than other diseases and NICE STA must work appropriately for rare diseases. Recent successes in extending rare disease treatments have been through the use of a managed access agreement to overcome uncertainties in the evidence. No explanation has been given to us about why this solution cannot be used here.

Finally, Sapropterin is used across the world and new developments in treatment are being trialled including in the UK. There is a clear unmet need for new treatment options for patients of all ages. It is hugely unfortunate that patients with PKU have waited 12 years to reach this point. You can make a huge difference to the lives of these patients and I therefore urge you to think again and extend the use of this life changing drug for adults who so desperately need our help.

Liz Twist MP
House of Commons

Mr Meindert Boysen
Director of the Centre for Health Technology Evaluation

Thursday 18th March 2021

Dear Mr Boysen,

Re: The public consultation on the use of sapropterin for Phenylketonuria

I am writing as Chair of the All Party Parliamentary Group for Phenylketonuria, along with many of my colleagues, to respond to the public consultation on the draft guidance for the use of sapropterin for PKU.

I have had the opportunity to meet families and individuals living with PKU and have gained an understanding of the extraordinary challenges of living with PKU. I welcome the recommendation to use sapropterin in children. However, I must express reservations about aspects of the guidance which I ask the Committee to consider.

1. First, the recommendation to cease treatment at age 18 should be re-considered. Withdrawing sapropterin treatment at age 18 when a young person is studying or starting an independent working life will be particularly difficult. The strict PKU diet is a drastically different dietary regime. Young people who have been prescribed sapropterin will struggle with a huge change to their diet and lifestyle when it is withdrawn and may not be able to control their phenylalanine levels. The draft guidance accepts that young people are still at risk of permanent brain damage as well as problems such as depression, anxiety and executive functioning deficits. The clinical justification for withdrawing treatment at 18 appears unsound. The Committee should take into account the concerns expressed by patients and families with PKU who truly understand what this draft guidance will mean. They are deeply concerned that withdrawing sapropterin treatment at 18 could have harmful effects on patient's physical and mental health – in effect the guidance risks setting up these young people to fail.

2. Further, we are concerned by the lack of provision for adults generally. We urge the Committee to reconsider the difficulties experienced by adults with PKU. We note that the draft guidance states that permanent brain damage can occur whilst the brain is still developing until "around age 25" but clinical experts suggest the brain continues to develop throughout life. Adult patients with PKU have told us of the debilitating effects of high phenylalanine levels on cognitive function and mental health. Clinical experts are also concerned that the higher incidences of co-morbidities experienced by people with PKU have not been properly accounted for in NICE's cost-effectiveness modelling, and that cognitive and mental health problems may have been undervalued.

3. There is concern that it is not appropriate to prevent clinicians from prescribing more than 10mg/kg if that is required for particular patients.

4. The failure to make a positive recommendation to support women with PKU to have access to sapropterin to support safe pregnancies is very concerning. The draft guidance accepts that the current NHS England commissioning arrangements for sapropterin in pregnancy are suboptimal as women cannot access the treatment prior to conception or in early

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pregnancy. Early pregnancy is a crucial time to prevent harm to the unborn child. The need to improve access is clear when we hear about the potentially devasting impact of uncontrolled phenylalanine levels on the developing baby. I note that the draft guidance particularly welcomes comments and further evidence on the experiences of women with PKU and their children and we urge the Committee to have regard to the intrinsic difficulties of collecting evidence about this sub-group of patients with a very rare condition. Collecting evidence of harm in pregnancy is particularly practically and ethically difficult. NICE must seek to overcome these difficulties to protect women and children.

5. We also ask the Committee to have regard to the wider issues affecting women with PKU in the development of its guidance. The patient group has conducted research which shows that PKU can cause fear and anxiety around sexual and reproductive health. Women also face challenges managing their condition whilst caring for young children. These issues may not attract much research, but it would be discriminatory if the Committee does not properly have regard to the experiences of this vulnerable group of women with a rare condition and their young children.

6. The interests of patients with learning disabilities should be reconsidered with care by the Committee. By definition, the PKU patient population includes many patients who have sustained brain damage or cognitive impairments. The draft guidance justifies refusing to make a positive recommendation for individuals with learning disorders or other special needs by reference to the cost effectiveness estimates; however these estimates are based upon the assumption that adults have the opportunity to utilise dietary treatment. Unfortunately this is not the case for many vulnerable adults with PKU.

7. We urge the Committee to approach this appraisal with realistic assumptions about the evidence base. PKU is a rare condition affecting the brain which may be less studied than other diseases and NICE STA must work appropriately for rare diseases. Many patients with PKU, and their families, are trying hard to participate in this consultation process to improve the guidance through their own lived experience. I urge the Committee to listen carefully to their feedback to ensure this guidance is robust and fair.

8. Finally, Sapropterin is used across the world and new developments in treatment are being trialled including in the UK. There is a clear unmet need for new treatment options for patients of all ages. It is unfortunate that patients with PKU have waited 12 years to reach this point. Sapropterin is the first advancement in care for PKU since dietary treatment was developed in the 1950s. I understand that NICE is able to have regard for the innovative nature of technologies when developing guidance and I urge you to consider the whole context in this case.

Yours sincerely,

Liz Twist.

Liz Twist MP
Member of Parliament for Blaydon

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Member of Parliament for Strangford

Marie Rimmer MP
Member of Parliament for St Helens South and Whiston

Catherine McKinnell MP
Member of Parliament for Newcastle upon Tyne North

Liz Saville Roberts MP
Member of Parliament for Dwyfor Meirionnydd

Peter Aldous MP
Member of Parliament for Waveney

Christina Rees MP
Member of Parliament for Neath

Neil Gray MP
Member of Parliament for Aidrie and Shotts

Tim Farron MP
Member of Parliament for Westmorland and Lonsdale

Sharon Hodgson MP
Member of Parliament for Washington and Sunderland West

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HOUSE OF COMMONS
LONDON SW1A 0AA

James Morris MP

Halesowen and Rowley Regis

Meindert Boysen,
Deputy Chief Executive, NICE

15th March 2021

Dear Mr Boysen,

RE: Public consultation on the draft guidance for the use of sapropterin for PKU

I am writing as Member of Parliament for Halesowen and Rowley Regis, to respond to the public consultation on the draft guidance for the use of sapropterin for PKU.

I have had the opportunity to meet families and individuals living with PKU and have gained an understanding of the extraordinary challenges of living with PKU. I also followed the PKU diet for a day, which gave me a huge insight to the struggles that families with children suffering from PKU have daily and also as an adult living with this illness.

I welcome the recommendation to use sapropterin in children, which is a great outcome for children in my constituency and across the country. However, I wish to raise the recommendation to cease treatment at age 18 and the implications this would have on a young adult's life as well as the lack of provision around adult treatment for PKU.

I am sure that you will take all considerations into account and I look forward to hearing from you in due course.

Yours sincerely,

James Morris MP

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ID1475 Sapropterin Consultation
National Institute for Health and Care Excellence
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Case Ref: DC14644

12 March 2021

Dear Sir/Madam

IS1475 Sapropterin Consultation

I am writing in support of my constituents, and to support the calls of the NSPKU to ensure that Sapropterin (Kuvan) can be made an available treatment option to all patients suffering from Phenylketonuria (PKU).

This draft guidance that proposes that Kuvan can only be prescribed for use in children up to the age of 18, has been described by the PKU community as both inappropriate and dangerous.

The risks of cognitive impairment and disability in children with uncontrolled PKU are accepted to be much greater. However, a committee of senior metabolic clinicians at NHS England noted that the risk of cognitive defects, depression, anxiety, white matter changes in the brain, low bone density and neurological impairments are still a significant risk for adult PKU sufferers.

Other than the use of Kuvan, the only other option for treatment is a highly restrictive dietary regime. For Kuvan to be withdrawn at 18 years old, patients will have been accustomed to a normalised diet and will lack the coping skills to control their phenylalanine levels. At this age, when teenagers will be finishing their education and potentially starting a more independent life, it is a cruel suggestion to withdraw the only known effective medical intervention available. It is also obscene that even where a patient's size and weight may indicate that a dose greater than 10mg would be more effective, that the dose would, under the current version of this draft guidance, be limited. Both these restrictions appear to be largely on the grounds of cost.

Some possible issues have been identified regarding the safety of Kuvan for those patients who are pregnant, and there may be legitimate concerns about the effectiveness for some PKU patients. However, I urge NICE to engage with expert clinicians, experts and stakeholders, such as the NSPKU, to ensure that this guidance is reviewed. Decisions on the use of this drug must be based on individual clinical assessment, and not an arbitrary age limit.

I would also request that due consideration is given to the specific concerns raised by the NSPKU with regard to those PKU patients with learning disabilities. These patients have often suffered brain damage as a result of delayed or sub-optimal treatment for PKU, and may be unable to control their condition effectively through conventional dietary management.

Yours faithfully,

Daisy Cooper MP
Member of Parliament for St Albans

PETER GIBSON MP

HOUSE OF COMMONS
LONDON SW1A 0AA

Professor Gillian Leng CBE
Chief Executive
National Institute for Health and Care Excellence
2nd Floor, 2 Redman Place
London E20 1JQ

Thursday 25 March 2021

Dear Professor Leng,

I am writing to you on behalf of the constituents of Darlington with Phenylketonuria (PKU) to respond to the public consultation on the draft guidance for the use of sapropterin for PKU.

I have had the opportunity to meet families and individuals living with PKU and have gained an understanding of the extraordinary challenges of living with PKU. I welcome the recommendation to use sapropterin in children. However I must express reservations about aspects of the guidance which I ask the Committee to consider:

1. First, the recommendation to cease treatment at age 18 should be re-considered. Withdrawing sapropterin treatment at age 18 when a young person is studying or starting an independent working life will be particularly difficult. The strict PKU diet is a drastically different dietary regime. Young people who have been prescribed sapropterin will struggle with a huge change to their diet and lifestyle when it is withdrawn and may not be able to control their phenylalanine levels. The draft guidance accepts that young people are still at risk of permanent brain damage as well as problems such as depression, anxiety and executive functioning deficits. The clinical justification for withdrawing treatment at 18 appears unsound. The Committee should take into account the concerns expressed by patients and families with PKU who truly understand what this draft guidance will mean. They are deeply concerned that withdrawing sapropterin treatment at 18 could have harmful effects on patient's physical and mental health – in effect the guidance risks setting up these young people to fail.
2. Further, we are concerned by the lack of provision for adults generally. We urge the Committee to reconsider the difficulties experienced by adults with PKU. We note that the draft guidance states that permanent brain damage can occur whilst the brain is still developing until "around age 25" but clinical experts suggest the brain continues to develop throughout life. Adult patients with PKU have told us of the debilitating effects of high phenylalanine levels on cognitive function and mental health. Clinical experts are also concerned that the higher incidences of co-morbidities experienced by people with PKU have not been properly accounted for in NICE's cost-effectiveness modelling, and that cognitive and mental health problems

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may have been undervalued.

3. There is concern that it is not appropriate to prevent clinicians from prescribing more than 10mg/kg if that is required for particular patients.
4. The failure to make a positive recommendation to support women with PKU to have access to sapropterin to support safe pregnancies is very concerning. The draft guidance accepts that the current NHS England commissioning arrangements for sapropterin in pregnancy are suboptimal as women cannot access the treatment prior to conception or in early pregnancy. Early pregnancy is a crucial time to prevent harm to the unborn child. The need to improve access is clear when we hear about the potentially devasting impact of uncontrolled phenylalanine levels on the developing baby. I note that the draft guidance particularly welcomes comments and further evidence on the experiences of women with PKU and their children and we urge the Committee to have regard to the intrinsic difficulties of collecting evidence about this sub-group of patients with a very rare condition. Collecting evidence of harm in pregnancy is particularly practically and ethically difficult. NICE must seek to overcome these difficulties to protect women and children.
5. We also ask the Committee to have regard to the wider issues affecting women with PKU in the development of its guidance. The patient group has conducted research which shows that PKU can cause fear and anxiety around sexual and reproductive health. Women also face challenges managing their condition whilst caring for young children. These issues may not attract much research, but it would be discriminatory if the Committee does not properly have regard to the experiences of this vulnerable group of women with a rare condition and their young children.
6. The interests of patients with learning disabilities should be reconsidered with care by the Committee. By definition, the PKU patient population includes many patients who have sustained brain damage or cognitive impairments. The draft guidance justifies refusing to make a positive recommendation for individuals with learning disorders or other special needs by reference to the cost effectiveness estimates; however these estimates are based upon the assumption that adults have the opportunity to utilise dietary treatment. Unfortunately this is not the case for many vulnerable adults with PKU.
7. We urge the Committee to approach this appraisal with realistic assumptions about the evidence base. PKU is a rare condition affecting the brain which may be less studied than other diseases and NICE STA must work appropriately for rare diseases. Many patients with PKU, and their families, are trying hard to participate in this consultation process to improve the guidance through their own lived experience. I urge the Committee to listen carefully to their feedback to ensure this guidance is robust and fair.
8. Finally, Sapropterin is used across the world and new developments in treatment are being trialled including in the UK. There is a clear unmet need for new treatment options for patients of all ages. It is hugely unfortunate that patients with PKU have waited 12 years to reach this point. Sapropterin is the first advancement in care for PKU since dietary treatment was developed in the 1950s. I understand that NICE is able to have regard to the innovative nature of technologies when developing guidance and I urge you to consider the whole context in this case.

I look forward to hearing from you in due course.

Yours sincerely,

PETER GIBSON MP

CC: Technology Appraisal Team 1, TAteam1@nice.org.uk

ERG critique of the company response to the ACD

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Sapropterin for treating phenylketonuria [ID1475]

Confidential until published

ERG critique of the company response to the ACD

This report was commissioned by the NIHR HTA Programme as project number 12/81/99

Completed 26th March 2021

CONTAINS ACADEMIC IN CONFIDENCE AND COMMERCIAL IN CONFIDENCE DATA

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent **(if you are responding as an individual rather than a registered stakeholder please leave blank):**	[**BioMarin International Limited**]
Disclosure **Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.**	[**No past, present direct or indirect link or funding from the tobacco industry**]

Name of commentator person completing form:	[Astrid Baumann, VP, Zone leader]
Comment number	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	In regard to the recommendation of sapropterin limited only to phenylketonuria (PKU) patients that are under 18 years of age, BioMarin (the Company) would like to state that all PKU patients, responding to treatment, could benefit from the sapropterin treatment. The health economic model that the company provided, indicates that for patients, below 18 years old, who start treatment and remain for lifetime, sapropterin is a cost-effective treatment in comparison to the standard of care when considering NICE's cost effectiveness thresholds. This finding is further confirmed in the new decision tree model that was submitted to the committee. The Company believes that this should be the correct interpretation of the data carried through into the policy.
ERG comment	The ERG does not consider that the company model is suitable for decision-making
2	In page 3, the appraisal consultation document states that *"there is no clinical trial or registry evidence to show whether sapropterin reduces the need for a protein-restricted diet or how it affects quality of life"*. The Company would like to state again that there are numerous publications showing that sapropterin treatment contributes to the decrease of the use of protein supplements. A list of relevant references follows in support to the Company's argument: • Yilmaz O, Quintana A, Rossi A, Dam E, Özel H, Rocha J, et al. Use of Special Medical Foods with Sapropterin in PKU, ESPKU conference 2018 (cross sectional survey) • Scala, I., Concolino, D., Casa, R.D. et al. Long-term follow-up of patients with phenylketonuria treated with tetrahydrobiopterin: a seven years' experience. Orphanet J Rare Dis 10, 14 (2015). https://doi.org/10.1186/s13023-015-0227-8 (no-profit open-label interventional trial) • Thiele AG, Weigel JF, Ziesch B, Rohde C, Mütze U, Ceglarek U, Thiery J, Müller AS, Kiess W, Beblo S. Nutritional Changes and Micronutrient Supply in Patients with Phenylketonuria Under Therapy with Tetrahydrobiopterin (BH(4)). JIMD Rep. 2013;9:31-40. doi: 10.1007/8904_2012_176. Epub 2012 Oct 17. PMID: 23430545; PMCID: PMC3565664. (open-label interventional trial) • Singh, R.H., Quirk, M.E., Douglas, T.D. et al. BH4 therapy impacts the nutrition status and intake in children with phenylketonuria: 2-year follow-up. J Inherit Metab Dis 33, 689–695 (2010). https://doi.org/10.1007/s10545-010-9224-1 (open-label interventional trial) • Burlina A, Blau N. Effect of BH(4) supplementation on phenylalanine tolerance. J Inherit Metab Dis. 2009 Feb;32(1):40-5. doi: 10.1007/s10545-008-0947-1. Epub 2008 Dec 9. PMID: 19067227. (retrospective clinical study) Furthermore, the long-term PKU registries, KAMPER in Europe and PKUDOS in the US, also shows that patients receiving sapropterin experience decrease in their blood phenylalanine (Phe) levels while their natural protein intake increases. (Muntau A, Lagler F, Feillet F, Alm J, Burlina A, Belanger-Quintana A, et al. Seventh Interim Analysis of the Kuvan® Adult Maternal Paediatric European Registry (KAMPER): Interim Results in Phenylketonuria Patients. Poster.; 2017, Longo N, Arnold GL, Pridjian G, Enns GM, Ficicioglu C, Parker S, et al. Long-term safety and efficacy of

	sapropterin: The PKUDOS registry experience. Mol Genet Metab. 2015;114(4):557-63). The above data has been corroborated by a panel of UK clinical experts that supported a minimum of 50% reduction in the use of protein supplements, potentially reaching 100% in highly responsive patients.
ERG comment	No comment
3	In page 4, the ACD states that "the dose of sapropterin is based on weight", the Company would like to clarify that it is the total daily dose that is based on weight. The dose per kg for a patient will not be affected if their weight is higher, all patients would remain on the same dose, i.e. 10 mg/kg regardless if they weight 20 or 70 kgs. It is the total daily dose that would increase.
ERG comment	No comment
4	In pages 4 and 21, the ACD states that "there is not enough evidence on how sapropterin might be used to prevent harm to the unborn child in women with PKU who are pregnant or trying to conceive" and "avoiding harm to the developing foetus was clearly important, and the committee welcomes comments and further evidence on the potential use of sapropterin in women with PKU of childbearing age, or those planning pregnancy, to prevent harm to the unborn child", respectively. The Company would like to clarify that the number of maternal PKU patients, if they are to be included in the policy, will be small. UK clinical experts estimate that there are approximately 50 to 60 PKU pregnancies per annum in the whole of UK. Of these pregnancies, it is estimated that the number of pregnant patients who will be in clinic and responsive is approximately 10 per annum. These patients might also require sapropterin treatment only for 6 to 9 months. The UK clinical experts have also confirmed that Phe tolerance increases as the foetus grows and starts to metabolise Phe itself which enables mothers to take more natural protein. In comparison to the life-time costs that would be associated with managing a child with PKU Syndrome, offering the option of sapropterin to pregnant PKU patients would result in negligible overall budget impact. Furthermore, the Company would like to provide further evidence to confirm that sapropterin is associated with the same benefits in terms of reduction in blood Phe levels and increased dietary Phe intake in the maternal PKU population as in the overall PKU population. PKUMOMS, the PKU in the Maternal Phenylketonuria Observational Program is a sub- registry of PKUDOS with two data cuts, in June 2013 and December 2018. The June 2013 data-cut of the PKU-MOMS sub-registry contained data from 21 pregnancies in women with PKU, five of whom were treated with sapropterin before pregnancy (but not during pregnancy), and 16 of whom were treated with sapropterin during pregnancy. Excluding data for spontaneous abortions (n = 4), the data show that the mean of the median blood Phe levels (204.7, SD: 126.6 µmol/L; n = 14) for women treated with sapropterin during pregnancy was 23% lower and had a 58% smaller standard deviation compared with the blood Phe (267.4, SD: 300.7 µmol/L; n = 3) for women who were not treated with sapropterin during pregnancy (i.e. treated prior to pregnancy group). Women on sapropterin during pregnancy experienced fewer blood Phe values above 360 µmol/L. When median blood Phe concentration was < 360 µmol/L throughout pregnancy, 75% (12/16) of pregnancy outcomes were normal versus 40% (2/5) of pregnancy outcomes when the median blood Phe was > 360 µmol/L. Grange et al. 2014, publication from PKU-MOMS, clearly shows that sapropterin during pregnancy leads to better Phe control. (Grange 2013) [redacted]

	[redacted] [redacted] [redacted] [redacted] Furthermore, additional publications including, Feillet 2014 and Nyuzuki 2019 further state that sapropterin use in pregnant woman leads to better blood Phe control and increased Phe tolerance. Feillet 2014 also reported the offspring of the seven pregnancies were all normal babies with normal birth measurements and outcomes. Nyuzuki 2019 reported normal growth and development of the child confirming the efficacy and safety of sapropterin in maternal PKU. International best practice guideline (Muntau 2019), also recommends sapropterin response testing for pregnant woman with PKU.
ERG comment	The ERG agrees with the wording of the ACD
5	In page 5, the ACD states that "childhood is the most critical period for brain development". The Company would like to state that brain development continues up to the age of 25 (which is also stated in page 6 of the consultation document), thus adolescence and early adulthood are also critical periods for brain development, education and social development. Furthermore, it has been widely demonstrated that adolescence and early adulthood are periods when Phe control becomes problematic.
ERG comment	No comment
6	In page 6, the ACD states that "Clinical experts estimated that 10% to 20% of patients struggle to maintain control of blood Phe levels". The Company would like to present data from Walter 2002 publication which show that adherence to a Phe-restricted diet is extremely challenging with as many as 75% of adolescents being unable to keep

	their blood Phe levels within the recommended target range. (Walter 2002) A similar observation from the US shows that Phe levels increase as age increases. This assessment of current management by Jurecki et al. included PKU clinics across the US in 2015 covering approximately 50% of PKU patients followed in clinics in the US showed that 12% of patients aged 0-4 years old had Phe levels higher than 360 µmol/L, 29% of patients aged 5-12 years old had Phe levels higher than 360 µmol/L and 40% of patients aged 13-17 years old had Phe levels higher than 360 µmol/L.
ERG comment	No comment
7	In page 6, the ACD states that "good control of blood Phe levels (below 200 micromols per litre) should be maintained if possible, but there are no strict guidelines or target Phe levels used in clinical practice". However, it is clearly stated in the 2017 EU Guidelines that pregnant PKU patients should maintain their Phe levels between 120 to 360 micromol/L (van Spronsen 2017) and UK clinical experts follow the European PKU guidelines.
ERG comment	No comment
8	In pages 17 and 18, the ACD states that "the model time horizon is not long enough to capture long-term brain damage in people with PKU and the model is not appropriate to capture the effects of PKU in pregnancy". The Company would like to state that owing to the teratogenic effects on children born to mothers with PKU, the model included an additional utility gain of [redacted] that sapropterin can potentially bring. This was presented to the Committee in the new decision tree model.
ERG comment	The [redacted] utility gain was arbitrarily determined and not supported by evidence
9	In page 19, the ACD states that "the ERG advised that the utility reductions may be double counted, because the reductions were already captured for different PKU symptom states". The Company would like to clarify that utility reductions have not been double counted. The health state vignettes that were presented to the general population in Sweden and clinical experts in England, did not include a description for intellectual disability and IQ deficits, hence inclusion of these in the decision tree model is not double counting.
ERG comment	The ERG considers that ambiguity remains
10	In page 19, the ACD states that "the ERG did acknowledge that increased blood Phe levels can harm the unborn child, but the extent of lost utility is unclear, as is the effect of sapropterin on that utility loss". The Company will like to recount 2 publications, Lenke et al. 1980 and Koch et al. 2003. High Phe concentration in PKU mothers crosses the placenta by active transport, resulting in 70% to 80% increased foetal concentration of Phe compared with maternal concentration. Elevated Phe is toxic and teratogenic to a developing foetus. Women of child-bearing age with high Phe during and before pregnancy leads to an increased risk of spontaneous miscarriage (24%), intrauterine growth retardation (40%), microcephaly (73%), global developmental delays (92%), and congenital heart defects (12%) in their offspring. These risk of teratogenic effects in offspring, can be potentially reduced by sapropterin use pre-conception and during pregnancy [Feillet 2014 and Nyuzuki 2019]. The decision tree model used an increase in utility of [redacted] to address this reduced long-term risk of abnormalities to the child.
ERG comment	The ERG agrees with the wording of the ACD
11	In page 21, the ACD states that "the committee concluded that escalation above the dose of 10 mg/kg for children and 12.5 mg/kg for adults would have a significant effect on the cost effectiveness of the treatment". The Company will like to state that in the ERG model that was presented to the committee, dose escalation from 10 mg/kg to 12.7 mg/kg had limited impact. The results are presented in the table below:

Age	Mean dosage	Mean cost per day	Reduction in daily PRD cost	Incremental daily cost	Annual incremental cost	Symptom severity	QALY incremental gain	IC Q ga
0-3 years	10mg/kg	[redacted]	£20.14	[redacted]	[redacted]	Mild	0.130	[redacted]
		[redacted]	£20.14	[redacted]	[redacted]	Moderate	0.134	[redacted]
		[redacted]	£20.14	[redacted]	[redacted]	Severe	0.145	[redacted]
	12.7mg/kg	[redacted]	£20.14	[redacted]	[redacted]	Mild	0.130	[redacted]
		[redacted]	£20.14	[redacted]	[redacted]	Moderate	0.134	[redacted]
		[redacted]	£20.14	[redacted]	[redacted]	Severe	0.145	[redacted]
0-17 years	10mg/kg	[redacted]	£22.41	[redacted]	[redacted]	Mild	0.130	[redacted]
		[redacted]	£22.41	[redacted]	[redacted]	Moderate	0.134	[redacted]
		[redacted]	£22.41	[redacted]	[redacted]	Severe	0.145	[redacted]
	12.7mg/kg	[redacted]	£22.41	[redacted]	[redacted]	Mild	0.130	[redacted]
		[redacted]	£22.41	[redacted]	[redacted]	Moderate	0.134	[redacted]
		[redacted]	£22.41	[redacted]	[redacted]	Severe	0.145	[redacted]

Furthermore, the new decision tree model submitted by the Company to the committee, the ICERs were:

Subgroups	Mean dosage(mg/kg/day)	Mean cost per day	Reduction in daily PRD cost	Incremental daily cost	Annual incremental cost	Symptom severity level
0-3 years	12.7mg/kg	[redacted]	£0.02	[redacted]	[redacted]	Mild
		[redacted]	£0.02	[redacted]	[redacted]	Moderate
		[redacted]	£0.02	[redacted]	[redacted]	Severe
0-17 years	12.7mg/kg	[redacted]	£0.02	[redacted]	[redacted]	Mild
		[redacted]	£0.02	[redacted]	[redacted]	Moderate
		[redacted]	£0.02	[redacted]	[redacted]	Severe

Thus, the dose increase to 12.7 mg/kg has shown limited impact on ICER for <18-year olds.

ERG comment	The ERG notes from the tables that increasing the dose of sapropterin leads to higher ICERs per QALY gained. Without access to the company model, the ERG cannot verify the data presented in the tables

ERG additional analyses (0 to 25 year patient population)

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Sapropterin for treating phenylketonuria [ID1475]

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ERG additional analyses (0 to 25 year patient population)

This report was commissioned by the NIHR HTA Programme as project number 12/81/99

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CONTAINS COMMERCIAL IN CONFIDENCE DATA

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A MEMBER OF THE RUSSELL GROUP

ADDITIONAL COST EFFECTIVENESS RESULTS REQUESTED BY THE NICE TEAM

Prior to the third NICE Appraisal Committee meeting, the NICE team asked the ERG to provide cost effectiveness results for the comparison of sapropterin versus protein restricted diet (PRD) only in a patient population aged between 0 and <25 years (i.e., up to the patient's 25th birthday) using the ERG's model and a daily dose of sapropterin of 10mg/kg for all patients. The ERG's ICERs per QALY gained are shown in Table 1. As the NICE Appraisal Committee has accepted that treatment with sapropterin reduces the need for a PRD, only the results that include a reduction in PRD are shown.

Sapropterin costs have been calculated using the average weight of patients aged between 0 and <25 years. The model also includes the average benefits of taking sapropterin (reduction in PRD costs and improvement in symptoms) for patients aged between 0 and <25 years. An average dose of 10mg/kg has been used, noting that the company provided evidence that the average dose for patients aged >18 years is 12.7mg/kg and the benefits for people aged between 18 and <25 years in the model are based on this higher dosage. Therefore, the assumption underpinning the presented cost effectiveness results is that doses of 10mg/kg and 12.7mg/kg are equally effective in the population aged between 18 and <25 years.

Table 1 ERG ICERs for a patient population aged between 0 and <25 years using the ERG model (PAS price for sapropterin)

Age	Mean sapropterin dosage	Mean sapropterin cost per day	Reduction in daily PRD cost with sapropterin	Incremental daily cost with sapropterin	Annual incremental cost with sapropterin	Symptom severity	QALY incremental gain with sapropterin	ICER per QALY gained with sapropterin
0 to <25 years	10mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	Mild	0.133	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Moderate	0.138	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Severe	0.155	[redacted]

ICER=incremental cost effectiveness ratio; PAS-Patient Access Scheme; PRD=protein restricted diet; QALY=quality adjusted life year

CONFIDENTIAL APPENDIX 2

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Sapropterin for treating phenylketonuria [ID1475]

Confidential appendix 2: cost effectiveness results generated using the discounted price of sapropterin

This report was commissioned by the NIHR HTA Programme as project number NIHR 128199

Completed July 14th 2021

COMERCIAL IN CONFIDENCE DATA REDACTED

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Sapropterin costs have been calculated using the average weight of patients aged between 0 and <25 years. The model also includes the average benefits of taking sapropterin (reduction in PRD costs and improvement in symptoms) for patients aged between 0 and <25 years. An average dose of 10mg/kg has been used, noting that the company provided evidence that the average dose for patients aged >18 years is 12.7mg/kg and the benefits for people aged between 18 and <25 years in the model are based on this higher dosage. Therefore, the assumption underpinning the presented cost effectiveness results is that doses of 10mg/kg and 12.7mg/kg are equally effective in the population aged between 18 and <25 years.

Table 1 71% reduction in PRD with sapropterin (PAS price)

Age	Mean sapropterin dosage	Mean sapropterin cost per day	Reduction in daily PRD cost with sapropterin	Incremental daily cost with sapropterin	Annual incremental cost with sapropterin	Symptom severity	QALY incremental gain with sapropterin	ICER per QALY gained with sapropterin
0-3 years	10.0mg/kg	[redacted]	£20.14	[redacted]	[redacted]	Mild	0.130	[redacted]
		[redacted]	£20.14	[redacted]	[redacted]	Moderate	0.134	[redacted]
		[redacted]	£20.14	[redacted]	[redacted]	Severe	0.145	[redacted]
	12.7mg/kg	[redacted]	£20.14	[redacted]	[redacted]	Mild	0.130	[redacted]
		[redacted]	£20.14	[redacted]	[redacted]	Moderate	0.134	[redacted]
		[redacted]	£20.14	[redacted]	[redacted]	Severe	0.145	[redacted]
0-17 years	10.0mg/kg	[redacted]	£22.41	[redacted]	[redacted]	Mild	0.130	[redacted]
		[redacted]	£22.41	[redacted]	[redacted]	Moderate	0.134	[redacted]
		[redacted]	£22.41	[redacted]	[redacted]	Severe	0.145	[redacted]
	12.7mg/kg	[redacted]	£22.41	[redacted]	[redacted]	Mild	0.130	[redacted]
		[redacted]	£22.41	[redacted]	[redacted]	Moderate	0.134	[redacted]
		[redacted]	£22.41	[redacted]	[redacted]	Severe	0.145	[redacted]
18-24 years	10.0mg/kg	[redacted]	£31.16	[redacted]	[redacted]	Mild	0.141	[redacted]
		[redacted]	£31.16	[redacted]	[redacted]	Moderate	0.148	[redacted]
		[redacted]	£31.16	[redacted]	[redacted]	Severe	0.180	[redacted]
	12.7mg/kg	[redacted]	£31.16	[redacted]	[redacted]	Mild	0.141	[redacted]
		[redacted]	£31.16	[redacted]	[redacted]	Moderate	0.148	[redacted]
		[redacted]	£31.16	[redacted]	[redacted]	Severe	0.180	[redacted]
<21 years	10.0mg/kg	[redacted]	£23.66	[redacted]	[redacted]	Mild	0.133	[redacted]
		[redacted]	£23.66	[redacted]	[redacted]	Moderate	0.138	[redacted]
		[redacted]	£23.66	[redacted]	[redacted]	Severe	0.155	[redacted]

Age	Mean sapropterin dosage	Mean sapropterin cost per day	Reduction in daily PRD cost with sapropterin	Incremental daily cost with sapropterin	Annual incremental cost with sapropterin	Symptom severity	QALY incremental gain with sapropterin	ICER per QALY gained with sapropterin
<22 years	10mg/kg	[redacted]	£24.00	[redacted]	[redacted]	Mild	0.133	[redacted]
		[redacted]	£24.00	[redacted]	[redacted]	Moderate	0.138	[redacted]
		[redacted]	£24.00	[redacted]	[redacted]	Severe	0.155	[redacted]
<23 years	10mg/kg	[redacted]	£24.31	[redacted]	[redacted]	Mild	0.133	[redacted]
		[redacted]	£24.31	[redacted]	[redacted]	Moderate	0.138	[redacted]
		[redacted]	£24.31	[redacted]	[redacted]	Severe	0.155	[redacted]
<24 years	10mg/kg	[redacted]	£24.60	[redacted]	[redacted]	Mild	0.133	[redacted]
		[redacted]	£24.60	[redacted]	[redacted]	Moderate	0.138	[redacted]
		[redacted]	£24.60	[redacted]	[redacted]	Severe	0.155	[redacted]
<25 years	10mg/kg	[redacted]	£24.86	[redacted]	[redacted]	Mild	0.133	[redacted]
		[redacted]	£24.86	[redacted]	[redacted]	Moderate	0.138	[redacted]
		[redacted]	£24.86	[redacted]	[redacted]	Severe	0.155	[redacted]

ICER=incremental cost effectiveness ratio; PRD=protein restricted diet; QALY=quality adjusted life year

ID1475 ACD consultation responses – thematic analysis

This document presents an overview of the thematic analysis conducted for the responses to the ACD consultation for the appraisal of sapropterin for treating PKU. This involved a qualitative analysis of all responses to the ACD to identify the main themes as well as recurring views associated with each theme. Of note, the qualitative analysis included both a semantic approach, which involved analysing the explicit content of the responses, and a latent approach, which involved reading into the subtext and interpreting the content of the responses.

In total, 401 responses were analysed as follows: 9 responses from experts and consultees, 55 responses from the public, 94 responses from the NICE web platform, and 243 responses from the NSPKU forum (117 for adult and 126 for children).

The main themes identified in the thematic analysis are presented alongside the proportion of responses for each theme from all responses. The themes are ordered according to proportion of mentions from highest to lowest proportion. With regards to the recurring views or subthemes, the proportions of mentions were calculated out of the number of responses which discussed the associated main theme.

Subthemes	Proportions of mentions
Stopping treatment with sapropterin at 18 years of age (92% of all 401 responses)	
Respondents disagreed, questioned or expressed concerns about the decision to stop treatment with sapropterin at 18.	95%

Subthemes	Proportions of mentions
Respondents described the decision to stop treatment at 18 as disruptive, unfair, unethical, dangerous, irresponsible, or distressing to young adults.	71%
Respondents suggested that treatment with sapropterin should be continued after 18 because PKU is 'for life' and so is the PKU diet according to clinical practice.	29%
Some respondents highlighted that they would not start sapropterin treatment for their children at all to avoid disruption and distress to their children's lives when reaching adulthood.	6%
Respondents indicated that sapropterin should be available for adults: • Up to 25 years of age • For life	 4% 76%
Respondents indicated that children lose the support of their parents and/or carers which leads to difficulties in managing the PKU diet on their own. Because of this and responsibilities of adulthood, managing the PKU diet becomes more difficult.	14% 12%
Respondents highlighted that stopping treatment with sapropterin at 18 will be challenging because: • Having lived all their life with the liberties and unrestricted diet that come with sapropterin treatment, young adults would have to learn how to manage the PKU diet from scratch with no experience or coping skills, which are normally developed during childhood and throughout teenage years. • Young adults may not be able to adhere to or manage the PKU diet due to a lack the lack of skills and coping mechanisms usually formed during childhood and teenage years. • Young adults may not be able to establish blood Phe control through dietary treatment, leading to PKU symptoms and potentially reducing their ability to manage the PKU diet.	 52% 33% 18% 12%

Subthemes	Proportions of mentions
• Young adults will not be accustomed to the taste or smell of the PKU diet and will have to adjust to tolerate low protein foods and protein substitutes. • Young adults are transitioning from children to adult clinical services, which are not equipped to educate adults or teach and instil the necessary skills to manage the PKU diet.	5%
Respondents highlighted that stopping treatment with sapropterin is likely to lead to additional demands on the healthcare system to: • Support people with PKU to manage the mental health effects of high Phe levels. • Support and educate people with PKU on how to manage the PKU diet. • Support people with PKU to achieve blood Phe control and reduce PKU symptoms	 5% 5% 4%
Respondents highlighted that stopping treatment with sapropterin will have a substantial impact on young adults' abilities to: • Live independently away from their parents' home. • Manage higher education studies. • Start and manage apprenticeships or jobs. • Undertake final exams and leave school. • Join and socialise with their peers. • Form personal relationships. • Start a family. Additionally, respondents also indicated that stopping treatment will have a detrimental impact on young adults': • Brain development	 32% 30% 27% 11% 8% 3% 2% 8%

Subthemes	Proportions of mentions
• Quality of life	3%
Occurrence of brain damage in adults (70% of all 401 responses)	
Respondents highlighted that NICE's statements about brain damage in adults are contradictory and that they do not agree with NICE's conclusions.	90%
Respondents felt that: • Patients with brain damage because of late diagnosis or because they had been advised to come off diet were being forgotten. • NICE ignored that the brain does not stop changing or developing throughout life.	 1% 8%
Respondents indicated that brain development continues: • In early adulthood • Until 25 years of age or beyond	 4% 26%
Respondents highlighted that brain damage occurs even in people with early-treated PKU and manifests as: • Cognitive impairments • Reduced executive function • Deteriorating mental health • Reductions in white matter • Grey matter abnormalities • Lower IQ scores than expected • Emotional difficulties	 6% 6% 6% 4% 2% 2% 2%
Respondents highlighted that:	

Subthemes	Proportions of mentions
• High blood Phe levels cause very serious symptoms and long-term effects on the brain. • The impact of blood Phe on the brain still largely unknown, but it is likely to be detrimental. • The brain damage experienced by people with PKU is not reversible or fully reversible.	9% 5% 4%
Impact of PKU and PKU diet on carers and family (61% of all 401 responses)	
Children with PKU	
Managing PKU and the PKU diet affects the entire family.	66%
Managing PKU and the PKU diet for children can have a substantial impact on parents': • Mental health • Quality of life. Respondents highlighted they experience a great deal of stress arising from managing their children's PKU symptoms, particularly mental health issues due to high Phe levels	 27% 12% 21%
Parents of children with PKU constantly feel concerns, guilt, stress and or anxiety about: • Managing the PKU diet and getting their children to adhere to it, particularly the aspect of force-feeding children supplements. • Children's mental and physical health. • Increased Phe levels in children and their effects children's health. • What children are eating outside of home or parents' supervision. • Children being or feeling isolated socially or being bullied because of their PKU. • Brain damage that might occur because of high Phe levels or not getting the diet right.	 26% 19% 18% 18% 14% 13%

Subthemes	Proportions of mentions
• Refusing children normal foods. • Explaining why their children cannot have normal foods.	13% 11%
Parents of children with PKU often have to: • Work reduced / part-time hours or seek flexible working arrangements. • Completely stop working or change careers to care for their children.	 24% 19%
Respondents highlighted that managing the PKU diet can be a whole job in itself because of the additional time needed to: • Shop for appropriate foods, read and understand labels, plan meals several days in advance and cook PKU friendly dishes using Phe-free ingredients (which are notoriously difficult to cook compared to normal ingredients) • Measure and monitor the amount of food eaten and left over to calculate the right number of exchanges. • Liaise with GPs, pharmacies and dietitians to advocate for their children and ensure prescriptions are fulfilled appropriately, arrive on time or include items of food that are more palatable. • Organise care such as blood tests, appointments with GPs, dietitians and psychologists, and daily reminders for children to take medication and supplements. • Educate self and children on PKU, foods that are safe to eat, how to cook PKU friendly foods and manage the diet appropriately. • Educate or train relatives, teachers, school cooks or other carers looking after their children on PKU and the PKU diet, and the importance of measuring everything their children eat as well as ensuring they do not eat any foods that a ‘forbidden’. • Plan any social gatherings such as birthday parties, meals out, play dates etc. or travelling abroad or domestically.	 35% 16% 13% 11% 7% 16% 34%

Subthemes	Proportions of mentions
The strain and stress of managing the PKU diet and dealing with symptoms resulting from high Phe levels can lead to arguments between family members, impact on relationships or even lead to break-ups and divorce.	10%
Siblings of children with PKU are also impacted by the condition and the PKU diet by: • Being deprived of normal activities such as meals out or eating normal foods as a family to protect to avoid isolating or making the child with PKU feel left out. • Receiving less attention from parents.	 8% 4%
Respondents reported that PKU and the PKU diet has a financial impact on the household income because of the reduction in working hours or career stops parents have to undertake to manage the diet and/or because of the additional costs incurred from buying prescription foods, trying to make the diet more varied or having to buy more expensive free-from foods.	21%
Adults with PKU	
Adults with PKU often require additional support from: • Relatives (parents, grandparents etc.) who help manage the PKU diet, either on a regular basis or when adults experience PKU symptoms due to high Phe. • Their partners who help manage the PKU diet (e.g., cooking, obtaining prescriptions, checking labels etc.) and provide support for dealing with PKU symptoms. • Their children who take on the role of carers and help with various aspects of the diet and PKU symptoms. Respondents indicated that they experience increased stress because of the PKU diet and PKU symptoms.	 7% 5% 1% 10%
PKU and the PKU diet impacts on families' ability to engage in social activities such as:	 7%

Subthemes	Proportions of mentions
• Eating out, because of the need for advance planning such as choosing as PKU-suitable restaurant and liaising with staff in advance to ensure they are equipped or willing to cater for an individual with PKU. • Travelling either domestically or internationally because of the high amount of prescription food needed to be packed.	5%
Respondents indicated that PKU, its associated symptoms and the PKU diet have led to: • Adults with PKU still living with family or having to move back because they were unable to manage the diet or deal with PKU symptoms on their own. • Strained family relationships, family arguments, break-ups or divorce. • Adults with PKU having reduced time or being unable to spend time with their children.	 5% 4% 2%
Maternal PKU (59% of all 401 responses)	
Respondents disagreed with or expressed concerns about the decision to not recommend treatment with sapropterin for women with PKU.	61%
Respondents felt that NICE have not taken women experiences into account when making their decision.	10%
The PKU diet recommended for safe pregnancies is even more restrictive than what women are used to, with nearly 0 allowance for protein.	17%
Women's experiences and thoughts about pregnancy are mostly associated with despondency because of: • Anxiety around the strictness of pregnancy diet • Effect of stress of pregnancy on mental health • Additional stress of diet on top of pregnancy issues that can arise • Terrifying thoughts of high Phe effects on unborn child	 31% 30% 29% 29%

Subthemes	Proportions of mentions
• Worry, stress and anxieties of unplanned pregnancy	21%
• Impact of pregnancy planning and success on romantic relationships and marriages	11%
• Need for considerations of abortions as option in case of maternal PKU syndrome or miscarriages	5%
• Discouragement from getting pregnant or instilment of fear of pregnancy by clinicians	5%
• Extreme guilt associated with high Phe effects on unborn child	4%
• Complexity and near impossibility of managing a job, the PKU diet and household or family duties	4%
• Inability to openly discuss pregnancy or ask for help	1%
Women with PKU are deterred from having children or even engaging in sexual activities or relationship because of the:	
• Fear, concerns or stress of high Phe effects on unborn child	16%
• Strict diet and low Phe levels needed for pregnancy	15%
• Extreme stress, guilt and/or shame of having a child with maternal PKU syndrome	11%
• Inability to maintain the ultra-low diet needed for pregnancy	10%
Women with PKU have difficulties achieving Phe levels suitable for pregnancy due to:	
• Severe illness	9%
• Nausea or sickness due to pregnancy	7%
• Complexity or strictness of PKU diet	4%
• Hormone changes	3%
• Prior suboptimal Phe control	3%
• Mental health	2%

Subthemes	Proportions of mentions
• Unpalatable supplements	2%
• Exhaustion	2%
• Eating disorders due to PKU diet	2%
• Learning disabilities	1%
The effects of maternal PKU syndrome on the unborn child are severe and can include:	
• Disability	9%
• Cardiac effects such as congenital heart disease	7%
• Microcephaly	5%
• Intellectual disability	5%
• Brain damage / neurological issues	5%
• Intrauterine growth	5%
• Brain damage / harm occurs in first 6 weeks of pregnancy	5%
• Delayed learning	3%
• Delayed development	3%
• Spontaneous abortion / miscarriage	3%
• Low birth weight	2%
• Congenital defects	2%
• ADHD	1%
• Autism spectrum disorder	1%
Respondents suggested that sapropterin should be available for:	

Subthemes	Proportions of mentions
• All women of childbearing age	52%
• Women who are trying to conceive	17%
• Women who are pregnant	17%
• After pregnancy	3%
Respondents indicated that treatment with sapropterin during and after pregnancy could:	
• Allow for better coping with PKU diet	10%
• Reduce the risk of high Phe levels to the unborn child	9%
• Help maintain low Phe levels	6%
• Reduce anxiety, stress and concerns around the effect of high Phe levels on the unborn child	5%
• Improve mood, reduce depression and enable women to better care for their newborn child	3%
Discriminatory draft guidance (55% of all 401 responses)	
Respondents felt that NICE had not considered treating people fairly and highlighted that the draft guidance was discriminatory on the basis of:	84%
• Age	35%
• Disability	23%
• Pregnancy or maternity	19%
• Sex	15%
• Ethnicity	8%
• Race	6%

Subthemes	Proportions of mentions
Respondents also indicated that treatment with sapropterin should be available to all people with PKU who respond to it.	48%
Living experience of adults with PKU (53% of all 401 responses)	
Respondents indicated that PKU and the PKU diet have a substantial effect on adults' ability to:	
• Manage work or staying in work	53%
• Engage in daily activities or day to day life	46%
• Maintain adequate mental health	31%
• Development of anxiety	29%
• Socialise or communicate clearly with peers, colleagues, friends and family	29%
• Manage or finishing studies	28%
• Advance in their careers of choice	24%
• Maintain or adhere to the PKU diet	22%
• Avoid obesity, eating disorders or gastrointestinal issues	20%
• Avoid depression, suicidal ideation or self-harm	17%
• Develop and maintain personal and romantic relationships	16%
• Live independently or manage a household	16%
• Maintain adequate quality of life	16%
• Maintain adequate blood Phe control	13%
• Maintain family relationships	12%
• Avoid stress	12%

Subthemes	Proportions of mentions
• Maintain physical health	11%
• Travel abroad or domestically or eat out with friends, family and peers	9%
• Having to explain PKU and the PKU to friends, co-workers, restaurant servers to be accommodated	9%
• Engage with clinical services or be able to advocate for themselves	7%
• Return to diet	6%
• Adjust their mood	6%
• Live a normal life	5%
• Get adequate nutrition from food	4%
Adults with PKU are disadvantaged by the condition and may struggle to maintain PKU diet because of:	
• Learning disabilities or difficulties	12%
• Cognitive impairments	6%
• Lower IQ scores	1%
• Neurological changes	1%
Adults with PKU frequently experience the following symptoms:	
• Low mood / mood swings / irritability / anger	38%
• Anxiety	37%
• Poor concentration or inability to focus	34%
• Brain fog	34%
• Depression	34%
• Fatigue, exhaustion, tiredness or lethargy	31%

Subthemes	Proportions of mentions
• Memory loss	28%
• Headaches or migraines	16%
• Tremors	9%
• Paranoia and/or agitation	6%
• Shakes	4%
• Pain	4%
• Low bone density	3%
• Low motivation	1%
Respondents highlighted that adults with PKU have additional needs in the form of:	
• Psychological support and/or therapy	12%
• Support from family, carers, friends and/or work colleagues	9%
• Counselling	8%
• Mental health support	8%
• Education on PKU diet	1%
Missing costs from cost-effectiveness model (43% of all 401 responses)	
Respondents indicated that the following health care system costs, which have not been included in the cost-effectiveness model, are substantial and should be considered:	
• Cost of any medications for PKU comorbidities such as anti-depressants, ADHD medications etc.	49%
• Cost of medical care of comorbidities, particularly psychiatric, psychology or counselling costs	53%
• Costs of maternal PKU and care for children with maternal PKU syndrome	51%

Subthemes	Proportions of mentions
• Costs of additional specialist care for PKU and diet side effects	29%
• Increased dietetic and health professional costs for poor metabolic control or nutritional deficiency	24%
• Speech therapy for babies with maternal PKU syndrome	16%
• Costs of care for patients with learning disabilities	16%
• Costs of dietary non-adherence of people with learning disabilities	12%
• Costs of nursing time for people with PKU in care homes	6%
• Dental costs	3%
• Costs of surgeries such as gallbladder removal, gastrotomy	2%
Respondents highlighted that community costs should also be included in the cost-effectiveness model such as:	
• Costs of GP or nurse visits	7%
• Cost of social services involvement for children with poor Phe control, early help or social care for children with maternal PKU syndrome	10%
• Costs of additional education and support in schools and university	21%
• Costs of extra educational needs for children with maternal PKU syndrome.	15%
Respondents indicated that patient and societal costs are also likely to be substantial and include:	
• Loss of earnings through time spent managing the diet	6%
• Loss of earnings through time spent caring for children with maternal PKU syndrome	3%
• Costs of Disability Living Allowance, Personal Independence Payments or Disabled Student Allowance	13%
• Loss of work productivity due to reductions in hours or stopping work altogether	8%

Subthemes	Proportions of mentions
• Reduced tax payments	3%
Experience of PKU diet (42% of all 401 responses)	
The PKU diet is not like a normal diet and can lead to the development of side effects such as: • Gastric or digestive issues • Disordered eating • Teeth issues such as tooth decay • Weight fluctuations • Nausea or vomiting • Mouth ulcers • Alopecia • Stunted growth • Pain • Irregular periods	 22% 10% 9% 8% 5% 2% 1% 1% 1% 1%
PKU diet alone does not prevent high Phe levels, which can occur because of illness, menstruation, stress, lack of eating or exercise.	25%
Patients were advised to come off the PKU diet according to past clinical practice and are struggling to return or adhere to the PKU diet as a result.	16%
Respondents felt that NICE had ignored the quality of life benefits of diet reduction for adults.	4%
Respondents indicated that the PKU diet is difficult to maintain, adhere to and even adjust to because of:	20%

Subthemes	Proportions of mentions
• Its time-consuming nature involving buying products from different shops to maintain variety, read and understand labels, cook with difficult ingredients, liaise with GPs and pharmacies to get the right prescription foods and in the correct amounts. • Unpalatable and badly smelling supplements • Acidic or bitter supplements • Few healthy or normal foods allowed in the diet • Increased costs to have variety of foods in the diet • Need to weigh and record all foods eaten • Constant feeling of hunger or satiety • Need to take monthly blood tests and organise prescriptions and shopping trips for PKU-friendly foods • The high-carbohydrate and sugar content of PKU foods and supplements • Inefficient absorption of synthetic amino acid supplements compared to natural amino acids.	17% 15% 15% 14% 13% 10% 8% 5% 1%
Respondents highlighted people with PKU struggle to maintain PKU diet or adhere to it consistently because of: • High Phe levels and PKU symptoms • Coming off diet in the past (on their own or due to clinician advice) • Cognitive impairments or disability • Complexity and strictness of diet • Few normal foods available • Expensive free-from foods and supplements • Lack of or reduced support from family, carers or health professionals	41% 24% 18% 16% 11% 11% 8%

Subthemes	Proportions of mentions
• Delayed access to or difficulty obtaining prescription foods • Full-time or shift work • Indisposition towards supplements or food neophobia • Lack of or limited access to kitchens, cooking equipment and/or prescription food storage space	6% 5% 4% 2%
Respondents indicated that the side effects of the PKU diet and the stress of having to constantly adhere to it can have an impact on: • Social interactions and socialising with friends, peers and family • Feeling isolated, left out or bullied or leading to self-isolation as a coping mechanism • Mental health • Academic performance • Physical health • Cognitive function • Ability to sleep • Concentration • Emotional capacity	 26% 23% 14% 9% 6% 5% 4% 3% 2%
Dose limit at 10 mg/kg (24% of all 401 responses)	
Respondents questioned the dose limit or indicated that it should not be imposed.	44%
Respondents felt that: • The dose of sapropterin should be based on individual needs and that the 20 mg/kg dose should be available to those who benefit from it.	55%

Subthemes	Proportions of mentions
• Doctors should have flexibility in prescribing sapropterin between 5 and 20 mg/kg according to the summary of product characteristics. • Restricting the dose to 10 mg/kg would lead to the exclusion of children who are responsive to higher doses. • The dose limit will reduce the effectiveness of sapropterin	53% 40% 15%
Some respondents highlighted need for clarity on how the dose will be administered in practice.	2%
Some respondents indicated that from personal experience an increase in dose to 20 mg/kg can have a dramatic effect on symptoms and diet relaxation.	2%
Comorbidities (13% of all 401 responses)	

Respondents indicated that people with PKU have additional comorbidities, which can make management of the PKU diet more difficult or affect quality of life:
• Effect on managing PKU diet
  ○ Depression
  ○ Anxiety
  ○ Learning disability
  ○ Gastrointestinal disorders
  ○ ADHD
  ○ Osteoporosis / osteoarthritis
  ○ Autism
  ○ Psychiatric conditions
  ○ Parkinson's disease
	76%
	
	35%
	30%
	17%
	15%
	11%
	9%
	7%
	7%
	4%

Subthemes	Proportions of mentions
○ Dementia	4%
○ Intracranial hypertension	4%
○ Down's syndrome	2%
○ Deafness	2%
• Effect on quality of life	
○ Diabetes / obesity	7%
○ COPD / asthma	6%
○ Polycystic ovaries	6%
○ Bulimia	6%
○ Body dysmorphia	4%
○ Anorexia	4%
○ Endometriosis	4%
○ Epilepsy	4%
○ Fibromyalgia	4%
○ Liver issues	4%
○ Alopecia	4%
○ Dermatillomania (excoriating disorder)	2%
○ Skin disease	2%
○ Subarachnoid brain haemorrhage	2%
○ Squashed pituitary gland	2%
○ Kidney issues	2%

Subthemes	Proportions of mentions
○ Psoriatic arthritis	2%
Some respondents also highlighted that people with PKU can have comorbidities resulting from high Phe levels: • Dyslexia • Spastic paraparesis • Peripheral nephropathy • Demyelination	 4% 2% 2% 2%
Sapropterin patent expiry and future generics (2% of all 401 responses)	
Respondents indicated that the patent exclusivity for sapropterin has expired and that generics are currently being produced, which are likely to be cheaper and therefore more cost-effective than Kuvan.	100%