Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
B12 Global Ltd	001	018 - 020	Where is the evidence that suggests pernicious anaemia (PA) is the most common cause of B12 deficiency? The NHS states this too, however in support groups of thousands of people it appears NOT to be the case. It is very hard to gain a diagnosis of PA due to low sensitivity of tests required to confirm lack of IF or IF antibodies. Has anyone investigated the prevalence of H pylori as a cause? Or explored inborn errors of B12 metabolism which are said to affect a huge number of the population. Many people were told they did not have PA during lockdowns of 2020 and were told simply had B12 deficiency so did not require B12 injections. This discrimination has been harmful.	Thank you for your comment. We have revised the introduction, made it more general to all vitamin B12 deficiency and removed the line stating that pernicious anaemia is the most common cause of B12 deficiency.
B12 Global Ltd	001	023 - 024	This is not always the case, macrocytosis not experienced by everyone with B12 deficiency. It can be a very late stage manifestation.	Thank you for your comment. We have revised the introduction, made it more general and removed reference to macrocytosis.
B12 Global Ltd	002	001	It would be very helpful to add depression/anxiety here, these are very common presenting symptoms.	Thank you for your comment. We have removed any reference to specific symptoms and made the statement quite brief. There are a are a lot of symptoms to consider and the list would be quite long. Symptoms will be covered in the review on the initial identification and assessment of vitamin B12 deficiency.
B12 Global Ltd	002	017 - 021	The most efficient and effective treatment of B12 deficiency is injections. Unless there is a proven dietary lack (and that is the only cause of the deficiency) injections will be the very	Thank you for your comment. The guideline will assess the effectiveness of different licenced modes of delivery for

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			best treatment. Subcutaneous injections should be considered here too. Many who self-inject use this form of administration.	vitamin B12 replacement and the effectiveness of self-administration of intramuscular vitamin B12 injections. We will review the evidence for the effectiveness of subcutaneous vitamin B12 injections. Should this be shown to be clinically and cost effective then the committee will be able to recommend its use as an off-label route of administration of subcutaneous vitamin B12 injections that are licensed for intramuscular injection. This reflects NICE processes which states off-label medicine is as "a medicine with an existing UK marketing authorisation that is: used outside the terms of its marketing authorisation, for example, by indication, dose, route or patient population; and it is not expected that the existing UK marketing authorisation will be extended to cover this use in the next 2 years.". We have amended our review question to investigate 'parenteral vitamin B12 replacement rather than just 'intramuscular' to reflect the question covers a wider range of interventions.
B12 Global Ltd	002	024	Could the term pernicious anaemia be changed to B12 deficiency as the symptoms are as serious and can lead to neurological complications– whatever the cause of the deficiency.	Thank you for your comment. We have revised this sentence to reflect that it relates to any vitamin B12 deficiency and that it is any complications.
B12 Global Ltd	002	026	Agreed, there needs to be more awareness that children and young people also have this deficiency.	Thank you for your comment.
B12 Global Ltd	005	020	The Active B12 Assay is not gold standard and will miss many B12 patients.	Thank you for your comment. This guideline will review the evidence for the diagnostic tests to use for vitamin B12 deficiency and make recommendations for diagnosis based on this evidence.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
B12 Global Ltd	006	019	Co factors should also be discussed for example folate.	Thank you for your comment. The guideline will include recommendations on what information to give people with vitamin B12 deficiency based on a review of the qualitative literature and the committee experience.
B12 Global Ltd	006	022	At the outset people need to understand that it is a serious condition and what the myriad symptoms can be (some people are totally unaware that B12 deficiency affects all body systems) and that if symptoms are not easing during loading doses that treatment frequency should be continued for the best chance of recovery. Information could be given to them for family members to be tested too.	Thank you for your comment. The guideline will include recommendations on what information to give people with vitamin B12 deficiency based on a review of the qualitative literature and the committee experience.
B12 Global Ltd	006	028	Signs and symptoms and family history of signs and symptoms for example poor mental health and cardiovascular events are key starting points. When B12 is found to be below range, some people are not treated at all but asked to come back in 2-3 months for another test. This is harmful.	Thank you for your comment. The review questions are draft and will be more clearly defined when the review protocols are set. Specific signs/symptoms/risk factors/comorbidities to be investigated will be agreed by the committee and pre-specified in the review protocols. The committee will consider these for inclusion in the protocol.
B12 Global Ltd	007	012	Adding testing for genetic methylation issues (MTHFR and MTRR at the very least) would be a great help to patients and doctors alike.	Thank you for your comment. The review questions are draft and will be more clearly defined when the review protocols are set. Specific tests to be investigated will be agreed by the committee and pre-specified in the review protocols.
B12 Global Ltd	007	022	B12 injections (at the frequency dictated by the patients need) would be the most cost effective and efficient route of administration. Oral tablets given inappropriately (when not solely dietary lack) just prolong the healing and can lead to permanent damage.	Thank you for your comment. The committee will review the evidence for the clinical and cost effectiveness of vitamin B12 replacement, including the dose, frequency and route of administration and make recommendations based on this evidence.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
B12 Global Ltd	007	026	If sub cut could be used, many patients would be able and happy to self-administer B12 injections, thereby drastically reducing the burden on nurses time in Practice or in the community. Afterall diabetics of all ages are trusted to self-administer insulin.	Thank you for your comment. Thank you for your comment. The guideline will assess the effectiveness of different licenced modes of delivery for vitamin B12 replacement and the effectiveness of self-administration of intramuscular vitamin B12 injections. We will review the evidence for the effectiveness of subcutaneous vitamin B12 injections. Should this be shown to be clinically and cost effective then the committee will be able to recommend its use as an off-label route of administration of subcutaneous vitamin B12 injections that are licensed for intramuscular injection. This reflects NICE processes which states off-label medicine is as "a medicine with an existing UK marketing authorisation that is: used outside the terms of its marketing authorisation, for example, by indication, dose, route or patient population; and it is not expected that the existing UK marketing authorisation will be extended to cover this use in the next 2 years.". We have amended our review question to investigate 'parenteral vitamin B12 replacement rather than just 'intramuscular' to reflect the question covers a wider range of interventions.
B12 Global Ltd	008	001	A check in on the patient during the first month would be pertinent. Seeing how loading doses improved symptoms or not, so that treatment frequency can be continued at a pace that is best for the patient.	Thank you for your comment. The committee will review the evidence in this area and then make recommendations accordingly.
B12 Global Ltd	008	003	Check that the patient is taking cofactors, folate etc. Checking iron levels. That the patient is experiencing improvement. No need to retest B levels, these will be	Thank you for your comment. The committee decide on the detail to include in the protocol, review the evidence in this area and then make recommendations accordingly.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			skewed. But if no response to treatment check reticulocyte count.	The committee will decide whether to review the evidence for retesting B12 or checking reticulocyte at follow up is a priority for this guideline.
British Society of Gastroenterology	001	018	This is probably too detailed now, but this emphasis on the autoimmune gastritis as by far the commonest cause of B12 deficiency is almost certainly incorrect. I am sure this will come out in the literature review, but this depends on whether this concerns just low B12 levels or clinically significant B12 deficiency	Thank you for your comment. We have revised the introduction, made it more general to all vitamin B12 deficiency and removed the line stating that pernicious anaemia is the most common cause of B12 deficiency.
British Society of Gastroenterology	001	020	Page 1 and also general Line 20 but general Throughout this document, as was apparent at the initial teleconference, the issue of what exactly is meant by pernicious anaemia is controversial and this really needs to be tightened up or much better definitions used. Pernicious anaemia strictly means the megaloblastic anaemia due to vitamin B12 deficiency that can sometimes be associated with catastrophic neurological compromise (hence "pernicious"). This can be due to any underlying case of vitamin B12 deficiency. Pernicious anaemia as used in this document seems to be implying the condition of autoimmune gastritis which can cause B12 deficiency. However, this is poor use of both non-technical and medical English language. The aetiology of the underlying condition is well understood (autoimmune gastritis), this is not always associated with either B12	Thank you for your comment. We have revised the introduction and made it more general to all vitamin B12 deficiency.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			deficiency, anaemia or neurological compromise and hence why continue to use a term "pernicious anaemia" for a condition (autoimmune gastritis) that is generally not pernicious and often not associated with anaemia and in fact affects a completely different organ? Whilst at the same time there are plenty of other conditions that can cause devastating B12 deficiency (hence truly pernicious) but are not the classical autoimmune disease previously labelled as pernicious anaemia.	
British Society of Gastroenterology	General	General	Regarding the proposed title change to "Vitamin B12 deficiency, including pernicious anaemia: diagnosis and management," I agree with the sentiment, but I feel strongly that the use of language is incorrect and misleading and sticking to Vitamin B12 deficiency, diagnosis and management would be better. This still covers all the relevant areas without seeming to focus on one incorrectly-termed disease. The change in title was added to ensure that the work and final document encompasses more of the wider aspects of the diagnosis and management of the common condition autoimmune gastritis (which is commonly but very incorrectly termed "pernicious anaemia") as well as the wider aspects of B12 deficiency due to other causes. The use of pernicious anaemia in the title is misleading because any cause of vitamin B12 deficiency can cause the pernicious megaloblastic anaemia and the treatment and management of true pernicious anaemia once it has occurred is very straightforward. Most of the work outlined	Thank you for comment. Several stakeholders commented on the content and title of the guideline and the consensus is that it should cover all forms of vitamin B12 deficiency. The final title of "Vitamin B12 deficiency, including pernicious anaemia: diagnosis and management" reflects the wider population and emphasises the original remit of pernicious anaemia. It is also what most stakeholders agreed with. The guideline will cover the diagnosis and management of all vitamin B12 deficiencies and therefore people with autoimmune gastritis will also be included. Pernicious anaemia is the generally accepted and widely used term whereas 'autoimmune gastritis is not widely used.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			in the draft concerns the management of B12 deficiency in patients that have never had, and will never get, pernicious anaemia (if we strict to the correct definition of pernicious anaemia). It seemed to me that the specific focus of the draft is actually directed to autoimmune gastritis with B12 deficiency. As most patients with autoimmune gastritis do not actually have anaemia, pernicious or otherwise, the title does give the incorrect emphasis. A title of Vitamin B12 deficiency: diagnosis and management, including autoimmune gastritis, would be better if there seems to be a strong undercurrent to focus on several of the issues directly related to this autoimmune gastritis group.	
British Society of Gastroenterology	General	General	There do not seem to be specific issues that the guideline should address regarding babies of mothers with a vitamin B12 deficiency	Thank you for your comment.
British Society of Gastroenterology	General	General	There do not seem to be specific cost saving interventions or examples of innovative approaches that should be considered for inclusion in this guideline. The main issues related to this concern the (1) most effective and cost-effective use of diagnostic tests, which should already be covered as outlined on page 7.	Thank you for your comment.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			(2) Most effective and cost-effective management and monitoring after starting treatment. This should already be covered as outlined on pages 7 and 8	
Cardiff Metropolitan University	001	005	In the title the emphasis has been taken away from PA, with guidelines now being written for all forms of B12 deficiency. The extent to which this guidance can be meaningful if it is generalizable to all forms of B12 deficiency is unclear. Support for individuals who have B12 deficiency arising from lifestyle influences (e.g. diet that is deficient in B12) would be appropriately managed via public health strategy. The guidelines would be more useful to clinical practice if they focused on the management of PA and other clinical forms of B12 deficiency. There are parallels that can be drawn from the long term and patient expereinces of a clinically caused B12 deficiency that may not present in deficiency that arises from diet. Suggested title "Guideline on the diagnosis and treatment of Pernicious Anaemia and other clinical forms of B12 deficiency)	Thank you for comment. We realise that the management of different causes of vitamin B12 deficiency need to be considered separately. The guideline reviews will be stratified by the cause of vitamin B12 deficiency to ensure that recommendations can be made for each cause where evidence permits. Several stakeholders commented on the content and title of the guideline and the consensus is that it should cover all forms of vitamin B12 deficiency. We have now changed the title to "Vitamin B12 deficiency, including pernicious anaemia: diagnosis and management".
Cardiff Metropolitan University	005	001	The management of general symptoms of B12 deficiency are not being addressed within the scope. This is problematic as the reliance on biological indictors of B12 deficiency as a guide for treatment effectiveness is flawed. Patient experiences recount that it is the general symptoms of the condition that they have the most difficulty managing,	Thank you for your comment. The guideline will investigate treatment of the vitamin B12 deficiency by focusing on the appropriate frequency, dose and route of vitamin B12 replacement and the impact this has on the person's quality of life.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			it is these symptoms that patients feel are minimised within general practice (see Seage , Glover and Mercer, 2019) . For guidelines to be effective they should support management of the condition in its entirety (not just in terms of serum B12 levels). A holistic approach to management is currently absent in standard care of B12 deficiency.	
Coeliac UK	005	012	We are pleased to see that the guidelines NG20 is included as a related guideline as investigation of people with B12 deficiency for coeliac disease will be an important aspect of this guideline.	Thank you for your comment.
Coeliac UK	007	010	We are pleased to see that identification of the cause of vitamin B12 deficiency will be a key point within this guideline. Investigation of the cause (including testing for coeliac disease) is important to ensure that people receive the necessary care.	Thank you for your comment.
De Montfort University	004	011	Specific consideration should be given to concurrent prescribed medication that can increase the risk of developing vitamin B12 deficiency, such as metformin and proton pump inhibitors as these are widely prescribed and are an often-overlooked risk factor.	Thank you for your comment. Medications that can increase the risk of developing vitamin B12 deficiency will be considered by the committee as part of the review protocol for this question.
De Montfort University	005	001	The scope currently excludes the management of symptoms related to vitamin B12 deficiency. The effective management of symptoms is an essential component of the holistic person-centred management of Pernicious Anaemia. The symptoms can be significantly disabling, distressing and have a negative impact on quality of life. Evidence-based recommendations to manage common	Thank you for your comment. The guideline will investigate treatment of the vitamin B12 deficiency by focusing on the appropriate frequency, dose and route of vitamin B12 replacement and the impact this has on the person's quality of life.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			symptoms should be included to avoid the potentially costly use of medications, investigations and treatments without a measurable benefit to patients.	
De Montfort University	005	004	The scope currently excludes the investigation and management of complications related to vitamin B12 deficiency. Many patients experience neurological symptoms, especially those that experienced a delay in diagnosis. These symptoms do not always resolve once appropriate treatment is commenced. Patients may undergo extensive investigations, such as MRI scans and nerve conduction studies relating to these symptoms- however, there is significant variation in practice relating to this. Including this aspect within these guidelines could significantly reduce costs of unnecessary investigations and treatments for complications, whilst also ensuring that appropriate investigations to exclude other neurological issues are not omitted.	Thank you for your comment. The guideline will investigate treatment of the vitamin B12 deficiency by focusing on the appropriate frequency, dose and route of vitamin B12 replacement and the impact this has on the person's quality of life. Complications will only be considered as an outcome in the treatment reviews.
De Montfort University	007	001	The scope currently excludes indicative symptoms as part of the diagnostic process for vitamin B12 deficiency. This would carry the risk that patients with borderline blood tests but significant symptoms may be overlooked. Literature recognises the lack of correlation in many cases between these diagnostic tests and the symptoms experienced by patients.	Thank you for your comment. The guideline will look at which symptoms suggest a vitamin B12 deficiency as well as which tests should be used. This does not necessarily exclude clinical assessment as part of this process.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
De Montfort University	008	003	The wording of this section currently appears focussed on haematological monitoring. The inclusion of symptom monitoring and assessment of quality of life is also recommended to ensure management is still meeting patient needs.	Thank you for your comment. The aim of this review is to look at the frequency and content of follow up. This will include the impact on quality of life and other outcomes which will be agreed by the committee when they set the protocol. We have changed the word 'monitoring' to 'follow up' to reflect this.
De Montfort University	General	General	If the guideline title is to be changed to include vitamin B12 deficiency it needs to be explicit throughout how these two conditions may differ. Whilst some vitamin B12 deficient patients without a current definitive diagnosis of Pernicious Anaemia due to a lack of positive antibody test, may actually have Pernicious Anaemia, a differentiation is still required within the guidelines as the treatment needed may be very different. Patients with a dietary vitamin B12 deficiency may have a reversible deficiency- and this needs to be explicit so that the life-long duration of Pernicious Anaemia is clearly stated. Different formulations and doses of replacement therapy may also be appropriate for these different conditions- so this would also need to be explicit.	Thank you for comment. Several stakeholders commented on the content and title of the guideline and the consensus is that it should cover all forms of vitamin B12 deficiency. We have now changed the title to "Vitamin B12 deficiency, including pernicious anaemia: diagnosis and management". The guideline will note the distinction on the different causes of vitamin B12 deficiency.. For each key area covered, where the committee agree that there is a clinical rationale, evidence will be stratified by cause of vitamin B12 deficiency. This will allow evidence for people with each cause of vitamin B12 deficiency to be reviewed separately and specific recommendations to be made for each group.
De Montfort University	General	General	The scope currently excludes whether private clinics and "wellness providers" are appropriate locations for the administration of vitamin B12 injections and infusions. These are now common, and their promotion of parenteral vitamin B12 to the general public can lead to confusion regarding the nature of a vitamin B12 deficiency.	Thank you for your comment. NICE guidelines are to provide recommendations for practice to the NHS, although private practice can choose to adopt the guideline. and regulators require that all registered professionals must be familiar with guidelines that affect their work. We are aware that private clinics and wellness providers offer vitamin B12 injections and infusions but we are only looking at the management of vitamin B12 deficiency within the NHS.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
Pernicious Anaemia Society (PAS)	001	005	New Title: I do not agree that the original remit of the Guideline be changed to include B12 Deficiency in general. There is a very real need for a guideline that clinicians can turn to for a specific disease in clinical practice. That is why this guideline is needed, to address and guide physicians on the diagnosis and management of Pernicious Anaemia. By addressing the problems with diagnosing this specific disease the issues surrounding wider B12 Deficiency will simultaneously be attended to; however, by dealing with the more general and wider issues with B12 Deficiency in general there is the very real danger that the issues with the diagnosis and treatment of Pernicious Anaemia will not be fully addressed. The issue of Vitamin B12 Deficiency in the general population is a public health matter due to socio-economic groups, age demographics, religion, lifestyle, culture and familial traditions. These issues could, and maybe should be addressed by a public information campaign and not by a clinical guideline. However, the ubiquitous fortification of everyday foodstuffs with B12 means that any deficiency is due to a problem with absorption, the problem is that the current assay used to determine the B12 status of patients is not really fit for purpose leading to a chronic problem of non-diagnosis or wrong diagnosis. Address the problem with diagnosing autoimmune Pernicious Anaemia and the issues with wider B12 deficiency would be simultaneously addressed. There is the danger that examining the issues surrounding general	Thank you for comment. Several stakeholders commented on the content and title of the guideline and the consensus is that it should cover all forms of vitamin B12 deficiency. We have now changed the title to "Vitamin B12 deficiency, including pernicious anaemia: diagnosis and management". We realise that the diagnosis and management of different causes of vitamin B12 deficiency need to be considered separately. The guideline reviews will be stratified by the cause of vitamin B12 deficiency to ensure that recommendations can be made for each cause where evidence permits.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			B12 Deficiency will leave the specific need for a clinical guideline on the biggest cause of deficiency unaddressed. 30% of the members of the PA Society waited five years or more to be diagnosed with 14% waiting over ten years for a correct diagnosis which more than proves the need for a specific guideline on the diagnosis and treatment of the disease (Hooper et.al. 2014). The James Lind Alliance Priority Setting Partnership on Pernicious Anaemia has seen over two hundred clinicians identifying 'uncertainties' with the diagnosis and treatment of Pernicious Anaemia which demonstrates the need, by doctors, for a clinical guideline on the disease. A better title would be **'Guideline on the diagnosis and treatment of Pernicious Anaemia and other non-Diet related B12 Deficiency'**.	
Pernicious Anaemia Society (PAS)	001	017	There is also the problem with modern medicines leading to the patient's B12 status being compromised (PPI's, Colchicine, Metformin, Contraceptive Pill etc). And, again, the UK's second most popular recreational drug, Nitrous Oxide and the use of 'Gas and Air' in childbirth also compromises the B12 status of patients.	Thank you for your comment. We have revised the introduction and made it more general to all vitamin B12 deficiency.
Pernicious Anaemia Society (PAS)	001	019 - 020	These figures are almost certainly inaccurate. This is because the assay used to determine the B12 status of patients has, over the last twenty years been changed from a more or less accurate algae-based assay to a molecular-based test that takes less time to be completed. If these figures relate to any analysis carried out over twenty years ago, they will be far more reliable than any more modern	Thank you for your comment. We have updated the figures.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			investigation. Similarly, the current assay used to determine whether any deficiency is due to Pernicious Anaemia – the competitive binding luminescence assay - is not fit for purpose rendering any modern statistics inaccurate. However, if the statistics relate to the period when the much more accurate Schilling Test was available then the figures would be much more reliable. Misdiagnosis is common which will compromise the accuracy of the statistics.	
Pernicious Anaemia Society (PAS)	001	022 - 023	This is a common misconception and the very first hurdle that has to be overcome in getting diagnosed. Only around 40-50% of patients deficient in B12 will have enlarged red blood cells. See the 2014 Guideline on Cobalamin and Folate Disorders by the British Committee for Standards in Haematology (BCSH). It is possible to have Pernicious Anaemia without any anaemia which is why some doctors consider Pernicious Anaemia to be a misnomer – perhaps Autoimmune Metaplastic Atrophic Gastritis would be a better name.	Thank you for your comment. We have revised the introduction and removed this statement.
Pernicious Anaemia Society (PAS)	002	014 - 016	If a deficiency is determined the patient is usually, though not always, interrogated as to whether the deficiency could be caused by diet (though the vast majority of vegans will be taking oral B12 supplements), surgery (though patients will have been prescribed replacement therapy injection to pre-empt any deficiency) or nitrous oxide abuse. If the deficiency cannot be attributable to the above then the deficiency will be due to malabsorption – Pernicious Anaemia or age-related gastric atrophy (ARGA). It will probably be due to autoimmune Pernicious Anaemia in	Thank you for your comment. The guideline scope covers identifying the cause of vitamin B12 deficiency. Within this key area of the scope evidence for the diagnostic accuracy and clinical and cost-effectiveness of tests will be reviewed, and recommendations will be made where possible. Clinical effectiveness will be assessed in the context of pre-specified, patient focussed outcomes, which the committee will agree upon when setting the review protocols.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			people who are not elderly though cases of ARGA will likely increase as the UK population ages.	
Pernicious Anaemia Society (PAS)	002	017 - 021	By far the most common calls to the PA Society's Telephone Helpline, online forum, email enquires relates to the treatment of Pernicious Anaemia. Again, the way in which patients with Pernicious Anaemia are treated differs from the treatment for other causes of B12 Deficiency (with the exception of gastric surgery and age-related atrophic gastritis). Treatment, as prescribed by the BNF has deteriorated in the past forty years in terms of frequency given. Treatment is far too often stopped (due to the clinician trying to monitor the serum B12 levels after injections have started or because another IF Antibody test is requested and returns as negative). Treatment varies enormously from clinic to clinic with some doctors prescribing injections according to the need of the patient while others stick rigidly to the one injection every three months. The PA Society were successful in getting the BNF to re-instate the two-monthly injection regimen in 2019. Patients who are unable to manage on the 'Feast and Fast' regimen either pay for private injections, or source injections from beaty parlours, internet 'pharmacies' or from pharmacies in other countries where they are available over the counter. There are issues of patient safety. Much better treatments such as slow-release preparations are available and in development in partnership with the PA Society. There has been no robust and long-term research into the efficacy of 1-2mg oral replacement therapy though some	Thank you for your comment. The guideline scope covers the management of vitamin B12 deficiency, including pernicious anaemia. Within this key area of the scope, evidence for the most clinically and cost-effective dose, frequency and route of administration of vitamin B12 replacement will be reviewed and recommendations will be made where possible. Clinical effectiveness will be assessed in the context of pre-specified, patient focussed outcomes, and stratifying the evidence by different populations will be considered which the committee will agree upon when setting the review protocols. We will make the committee aware of your comment.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			patients with PA have reported a preference for such treatment. The problem is how is the efficacy measured – simply looking for improvement in the blood picture is not enough as the B12 assay is unreliable and evaluating the size of the red blood cells wouldn't necessarily work as the patient may very well not have had any enlarged cells at diagnosis. A better indicator would by using a Functional Outcome Score which is in development by the society and a team of psychologists and pharmacists from a university.	
Pernicious Anaemia Society (PAS)	002	022	There is a growing awareness of B12 Deficiency – see social media sites. What is more important is the development of a better assay, or series of assays, to accurately assess not only the B12 status of patients, but also whether the deficiency is due to lack of intrinsic factor or intrinsic factor antibody. This would result in far more people being identified as being deficient in B12 and given an explanation of their deficiency. Because of the ubiquitous use of B12 fortification in foods, and the increasing use of daily multivitamin supplements that contain B12, (worth £430.3 million in the UK per annum) it's obvious that most people with B12 deficiency will have Pernicious Anaemia by any other name.	Thank you for your comment. Developing better assays is beyond the remit of this guideline but we will seek to assess the diagnostic accuracy and effectiveness of tests in helping determine the cause of vitamin B12 deficiency.
Pernicious Anaemia Society (PAS)	003	019	There is a vast knowledge gap in infantile and juvenile Pernicious Anaemia. Children being under-treated often struggle in school where they risk being labelled as having 'behavioural problems' or Special Educational Needs. Parents who inject their children between their two or three-monthly injections given at a surgery risk being charged	Thank you for your comment. The guideline aims to recommend best practice. Self (or parent) administration of vitamin B12 replacement will be covered. If the guideline recommends its use in children this should be taken into account before any parent is charged with abusing their child.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			with Actual Bodily Harm or Child Abuse. The PA Society is aware of a number of cases where the parent is diagnosed as having Munchausen by Proxy. The society is also aware of children being taken into care.	
Pernicious Anaemia Society (PAS)	003	021	There is a compelling case for the screening of pregnant women to determine their B12 status (though this is difficult using the current assay used to do so). This is because of two things. Firstly, if a mother-to-be is deficient in both B12 and Folate, addressing the Folate deficiency without rectifying any B12 deficiency will lead to the 'folate trap' whereby any future supplementation of B12 – whether orally or by injections – will not have any effect on the well-being of the patient. Secondly, the raising of the Upper Tolerable Level of the mandatory fortification of flour with folic acid will undoubtedly increase the problem with the 'folate trap' in the future.	Thank you for your comment. Policy on screening of all pregnant women is decided by the UK National Screening Committee, not by NICE. However, pregnant women in whom there is reason to suspect vitamin B12 deficiency will be covered by this guideline.
Pernicious Anaemia Society (PAS)	004	011	Again, there is a real distinction here between Pernicious Anaemia and more general B12 Deficiency. PA is an autoimmune disease and patients with the disease will often have two to four other autoimmune diseases, the most common being Psoriasis (which many patients report as improving after having B12 injections), Hashimoto's, Type 1 Diabetes and Rheumatoid Arthritis. Though not an autoimmune disease by far the most common co-existing condition with PA is Tinnitus – so common that it could be seen as a reliable symptom. Patients with other autoimmune diseases who have B12 deficiency could very well have Pernicious Anaemia.	Thank you for your comment. Autoimmune diseases and tinnitus will be considered by the committee when writing the protocol for the review on risk factors for vitamin B12 deficiency.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
Pernicious Anaemia Society (PAS)	004	013 - 017	Over the past twenty-thirty years the assays for evaluating the B12 status of patients and whether the deficiency is due to Pernicious Anaemia have become much less reliable. Both assays lack specificity. There are better assays available which are either more costly (Active B12 + MMA + Homocysteine) or are no longer considered to be safe in hospital laboratories (Schilling Test). Addressing the problems with these assays will be the biggest challenge for this guideline. Again, see the BCSH Guideline from 2014.	Thank you for your comment. The tests included in the evidence reviews on diagnostic tests and tests to identify the cause of vitamin B12 deficiency will be agreed by the committee when the review protocol is set.
Pernicious Anaemia Society (PAS)	004	018	Giving the patient a choice of treatment, including sub-cutaneous self-administered injection, is an objective of the PA Society. However, we agree with the BCSH that at diagnosis the patient be given loading doses of injections before being given a choice of future treatment. Indeed, more and more GPs are now teaching their patients how to self-administer injections of B12 that are guaranteed to be of pharmaceutical standards. During the Covid-19 pandemic self-administered injections was suggested by the RCGP as an option to cut footfall to surgeries and health centres. This area is where there is greatest scope for cost savings in the NHS. There is, however, the ongoing problem of monitoring the efficacy of treatment as looking at the blood picture would not be worthwhile as it would only tell part of the story. The patient experience is the most important indicator of the efficacy of treatment. There is one other issue that should be noted. Some patients, although these are very few, are unable to tolerate any cobalamin supplements, even in the smallest amounts	Thank you for your comment. The guideline will assess the effectiveness of different licenced modes of delivery for vitamin B12 replacement and the effectiveness of self-administration of intramuscular vitamin B12 injections. We will review the evidence for the effectiveness of subcutaneous vitamin B12 injections. Should this be shown to be clinically and cost effective then the committee will be able to recommend its use as an off-label route of administration of subcutaneous vitamin B12 injections that are licensed for intramuscular injection. This reflects NICE processes which states off-label medicine is as "a medicine with an existing UK marketing authorisation that is: used outside the terms of its marketing authorisation, for example, by indication, dose, route or patient population; and it is not expected that the existing UK marketing authorisation will be extended to cover this use in the next 2 years.". We have amended our review question to investigate 'parenteral

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			and no matter how the supplement is administered. There is no longer any expert in sensitising patients to cobalamin – and so the only option available to these patients who rely on supplements to keep them alive (if they have PA) is to eat cooked shellfish, raw to lightly cooked offal or highly concentrated beef liver extract.	vitamin B12 replacement rather than just 'intramuscular' to reflect the question covers a wider range of interventions. With regard to intolerance to cobalamin supplements as this is such a rare event and the only alternative treatment options are food sources with a high concentration of vitamin B12 we have not prioritised this for inclusion in the guideline.
Pernicious Anaemia Society (PAS)	004	025	There is evidence, both scientific and verbally reported, that Methylcobalamin repairs damage to the Myelin sheath and is the preferred type of B12 used by those patients with PA who self-inject. Methylcobalamin is not licensed in the UK but it is widely available on the internet or in Far East pharmacies.	Thank you for your comment. Before NICE can recommend medicines, they need to have been assessed by the MHRA as safe and given a UK licence. Without this approval, we cannot include them in the guideline.
Pernicious Anaemia Society (PAS)	006	006	Poor assays lead to repeated visits to Primary care clinics, misdiagnosis, non-diagnosis and years of ill health. But there are other economic costs involved. Secondary consultations (usually to haematologists) are usually futile, as are the various expensive tests such as MRI scans, Nerve Conduction Tests and CT scans. There is, to date, no data on how much these secondary consultations and test cost the NHS but the figure is likely to be high. The PA Society is in a unique position to comment on the other socio-economic costs such as taking time off work to visit a nurse for the (usually much needed) injection; underperformance in the workplace or in education along with the costs of relationship breakdowns. All are consequences of Pernicious Anaemia that the society deals with on a day-to-day basis.	Thank you for your comment. These points will be considered when prioritising areas for economic modelling, and for inclusion in any model in the guideline.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
Pernicious Anaemia Society (PAS)	006	022	Patients need to be told that: a. Their replacement therapy injections are for life and should never be stopped b. There is no further testing needed once injections are started as it is not possible to monitor B12 levels without the risk of resulting nerve damage if injections are stopped and then wait for levels to become low again c. They need to urgently revisit their physician if they experience any pins and needles, numbness, unsteady or unusual gait or balance issues If the patient already has neurological issues then he or she should be told that they will receive injections of B12 'every other day until there is no further improvement' (British National Formulary).	Thank you for your comment. The guideline will include recommendations on what information to give people with vitamin B12 deficiency based on a review of the qualitative literature and the committee experience.
Pernicious Anaemia/B12 Deficiency Support Group	001	005	We agree to the proposed title change to "Vitamin B12 deficiency, including pernicious anaemia: diagnosis and management" as we feel this better reflects the wider array of causes of vitamin B12 deficiency and recognises that all these causes have the same serious and potentially life threatening results without treatment.	Thank you for comment. Several stakeholders commented on the content and title of the guideline and the consensus is that it should cover all forms of vitamin B12 deficiency. We have now changed the title to "Vitamin B12 deficiency, including pernicious anaemia: diagnosis and management".
Pernicious Anaemia/B12 Deficiency Support Group	001	017	One major and three significant causes of B12 deficiency are missing here – drug-induced (e.g. use of proton pump inhibitors, metformin), genetic (e.g. transcobalamin deficiency) and infection (H. Pylori, Small Intestine Bacterial Overgrowth/SIBO, tapeworm).	Thank you for your comment. We have revised the introduction and made it more general to all vitamin B12 deficiency.
Pernicious Anaemia/B12	001	023	Neurological and psychiatric symptoms as well as fatigue are the first and most commonly experienced symptoms by our members (over 90% had one or both on a recent survey	Thank you for your comment. We have revised the introduction, made it more general and removed reference to macrocytosis.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
Deficiency Support Group			of 1500+ members). Macrocytosis and anaemia are late stage symptoms and not present in a significant proportion of patients (just 30% of our members had either of these on the same survey), so the absence definitely does not exclude B12 deficiency. We would like to see this section reworded to place more emphasis on neurological and psychiatric symptoms, as well as fatigue, as they are the most likely to be the initial presenting symptoms, as well as being the most troublesome symptoms for the patient.	
Pernicious Anaemia/B12 Deficiency Support Group	002	001	We agree that symptoms are non-specific – it might be helpful to mention that symptoms are wide-ranging as it affects all systems of the body at a cellular level, particularly both the central and peripheral nervous systems. Neuropsychiatric symptoms, such as depression or dementia, and balance problems (e.g. frequent falls in the elderly population) are two very common symptoms not mentioned here.	Thank you for your comment. We have removed any reference to specific symptoms and made the statement quite brief. There are a are a lot of symptoms to consider and the list would be quite long. Symptoms will be covered in the review on the initial identification and assessment of vitamin B12 deficiency.
Pernicious Anaemia/B12 Deficiency Support Group	002	004	Vitamin B12 deficiency significantly increases cardiovascular risk, e.g. strokes, heart disease, blood clots (due to effects on homocysteine) and is fatal if untreated. Non-alcoholic fatty liver disease is common and there is also an increased risk of gallstones due to increased turnover of red blood cells. Untreated or under-treated patients with severe psychiatric symptoms of B12 deficiency are at risk of self-harm and suicide.	Thank you for your comment. We have removed any reference to specific symptoms and made the statement quite brief. There are a are a lot of symptoms to consider and the list would be quite long. Symptoms will be covered in the review on the initial identification and assessment of vitamin B12 deficiency.
Pernicious Anaemia/B12	002	010	The full blood count is not a reliable test for vitamin B12 deficiency as macrocytosis is not present in a significant number of patients and can be masked by folic acid	Thank you for your comment. The guideline scope covers diagnosing vitamin B12 deficiency. Within this key area of the scope evidence for the diagnostic accuracy and clinical

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
Deficiency Support Group			supplementation. Macrocytosis can also be masked by concurrent microcytosis due to iron deficiency, as well as occurring in some other conditions such as thyroid disease and alcoholism.	and cost-effectiveness of tests will be reviewed, and recommendations will be made where possible. Clinical effectiveness will be assessed in the context of pre-specified, patient focussed outcomes, which the committee will agree upon when setting the review protocols.
Pernicious Anaemia/B12 Deficiency Support Group	002	014	We agree with this – blood tests for intrinsic factor antibodies in particular have a low sensitivity (60%), leaving patients that are unable to absorb vitamin B12 without a formal diagnosis and negatively affecting access to lifesaving injections. Useful tests are intrinsic factor antibodies, parietal cell antibodies, serum gastrin, active B12 (holotranscobalamin), methylmalonic acid (MMA), homocysteine and unsaturated B12 binding capacity (UBBC), which can identify transcobalamin 1 Deficiency. Gastroscopy with duodenal biopsy is useful for identifying gastritis and/or coeliac disease. Negative tests still do not exclude an absorption problem with vitamin B12.	Thank you for your comment. The guideline scope covers identifying the cause of vitamin B12 deficiency. Within this key area of the scope evidence for the diagnostic accuracy and clinical and cost-effectiveness of tests will be reviewed, and recommendations will be made where possible. Clinical effectiveness will be assessed in the context of pre-specified, patient focussed outcomes, which the committee will agree upon when setting the review protocols.
Pernicious Anaemia/B12 Deficiency Support Group	002	018	It's not just patients with pernicious anaemia that require injections – all those with an inability to absorb vitamin B12 in their diet require injections. It would be far more useful to differentiate between those who do not consume enough B12 in their diet and those who cannot absorb vitamin B12. NB A negative intrinsic factor antibody test does not mean that a patient has a dietary deficiency. Patients consuming foods containing B12 several times a week (e.g. meat, fish, eggs, dairy, fortified foods) have sufficient B12 in their diet, so any deficiency will be due to a problem with absorption. Those with insufficient B12 in their diet have at least the	Thank you for your comment. We have revised the introduction and made it more generic for vitamin B12 deficiency. The guideline will differentiate between those who do not consume enough B!2 in their diet and those who cannot absorb vitamin B12. The guideline scope covers identifying the cause of vitamin B12 deficiency. Within this key area of the scope, evidence for the diagnostic accuracy and most clinically and cost-effective tests will be reviewed and recommendations will be made where possible. Clinical effectiveness will be assessed in the context of pre-specified,

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			same risk of developing an underlying absorption problem with B12 as the general population, so non-dietary causes of B12 deficiency should also be considered, especially if symptoms do not resolve quickly with oral treatment.	patient focussed outcomes, which the committee will agree upon when setting the review protocols.
Pernicious Anaemia/B12 Deficiency Support Group	002	019	Injections given in a medical setting are more costly than oral treatment; however the costs of untreated, under-treated or inappropriately treated B12 deficiency are staggeringly huge. Medications such as anti-depressants, painkillers for nerve pain (e.g. gabapentin) and extreme fatigue (e.g. modafinil) are often prescribed to treat the symptoms of B12 deficiency when vitamin B12 injections would be cheaper, safer and more effective, and with no risk of addiction. There would be reduced diagnosis and referral costs, particularly referrals and investigations (e.g. MRIs) for neurological symptoms, and a reduction in unnecessary surgeries (e.g. carpal tunnel release). Reduction in homocysteine reduces cardiovascular risk in these patients and expensive inpatient treatment for stroke, myocardial infarction and pulmonary embolism, as well as long term disability. Many patients with B12 deficiency experience significant symptoms affecting activities of daily living and quality of life on the standard treatment of every 2-3 months. Increasing injections for these patients has the potential to reduce symptoms and long term disability, and the resulting financial drain on medical and social care. In addition, switching to self-administration of vitamin B12 injections for the majority of patients would be even cheaper and compares very favourably from a cost point of view. For	Thank you for your comment. The dose, frequency and route of administration of vitamin B12 replacement will be reviewed within the guideline as will self administration. The committee will also discuss whether this is a suitable area to prioritise for economic modelling.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			example, a patient was prescribed anti-depressants, gabapentin and modafinil over a 12 year period at a cost of £25,000 just for the medication, which did not adequately relieve symptoms and the patient was unable to hold down full time employment and struggled with activities of daily living. When this patient switched to every other day injections (as appropriate for treating neurological symptoms of B12 deficiency), huge and sustained improvements in symptoms occurred, enabling the patient to return to a normal life and full time employment. The approximate cost for self-administered every other day injections over the same time period would have been just £3000.	
Pernicious Anaemia/B12 Deficiency Support Group	002	021	We would support the use of subcutaneous injections instead of intramuscular injections – these are better tolerated by patients, easier for self-administration and the feedback from our group members is that these are just as effective as intramuscular injections. Available formulations of B12 in the UK are also sold in the EU in different packaging over the counter without a prescription and licensed for intramuscular, subcutaneous and intravenous use. We do not support oral treatment for patients with a vitamin B12 absorption issue – the clinical evidence does not support this as a valid treatment option and risks worsening neurological damage, disability and death in a population already struggling to access sufficient injections. The studies often quoted as supporting oral treatment are based	Thank you for your comment. The guideline will assess the effectiveness of different licenced modes of delivery for vitamin B12 replacement and the effectiveness of self-administration of intramuscular vitamin B12 injections. We will review the evidence for the effectiveness of subcutaneous vitamin B12 injections. Should this be shown to be clinically and cost effective then the committee will be able to recommend its use as an off-label route of administration of subcutaneous vitamin B12 injections that are licensed for intramuscular injection. This reflects NICE processes which states off-label medicine is as "a medicine with an existing UK marketing authorisation that is: used outside the terms of its marketing authorisation, for example, by indication, dose, route or patient population; and it is not

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			on a population without proven B12 absorption problems, held over a short period of time, and do not measure the effect on symptoms. Oral treatment does not compare favourably on cost compared to self-administered injections either, with a 30 day supply of tablets being nearly twice as expensive as an equivalent 30 day supply of hydroxocobalamin ampoules for every other day injection. The recent Covid pandemic caused significant changes in treatment for patients. Those patients who had their injections reduced reported significant increases in symptoms and reduction in quality of life, and major dissatisfaction with their care, which was even worse for those who were switched to oral treatment. Conversely, those who were switched to self-administration of injections reported significant improvements in symptoms and quality of life, and much preferred this route as they had more control of their own treatment. No adverse effects as a result of self-administration of injections were reported.	expected that the existing UK marketing authorisation will be extended to cover this use in the next 2 years.". We have amended our review question to investigate 'parenteral vitamin B12 replacement rather than just 'intramuscular' to reflect the question covers a wider range of interventions.
Pernicious Anaemia/B12 Deficiency Support Group	002	022	We fully agree here – also improved management would significantly improve patient outcomes.	Thank you for your comment.
Pernicious Anaemia/B12 Deficiency Support Group	002	024	Not just pernicious anaemia – all causes of B12 deficiency will lead to neurological and other serious or fatal complications.	Thank you for your comment. We have revised this sentence to reflect that it relates to any vitamin B12 deficiency and that it is any complications.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
Pernicious Anaemia/B12 Deficiency Support Group	002	025	We agree – vitamin B12 deficiency is poorly recognised in children and young people and management is affected by the lack of clear guidelines here. Early diagnosis and pro-active treatment is necessary to prevent permanent long term damage to the developing brain.	Thank you for your comment.
Pernicious Anaemia/B12 Deficiency Support Group	003	002	Will the new guidelines have an impact on health education providers, e.g. medical and nursing schools to ensure that future health practitioners do not have a knowledge gap?	Thank you for your comment. It will be up to health education providers to decide whether to include this NICE guideline in their teaching.
Pernicious Anaemia/B12 Deficiency Support Group	003	010	We would like to include disability here, particularly with regards to mental health – those of our members with psychiatric symptoms due to B12 deficiency or who have a pre-existing psychiatric comorbidity frequently report unsatisfactory interactions with health professionals as both physical and psychiatric symptoms are attributed to poor mental health. E.g. pins and needles being attributed to anxiety rather than identified as due to vitamin B12 deficiency related nerve damage.	Thank you for your comment. We have added disability here.
Pernicious Anaemia/B12 Deficiency Support Group	003	021	Pregnant and breastfeeding women require additional B12 to support the baby's development as well as their own health, so injections may need to be increased during this time. Use of nitrous oxide is strongly contraindicated with vitamin B12 deficiency (even in patients on injections) as it inactivates all circulating vitamin B12, which can precipitate subacute combined degeneration of the cord. Given the high incidence of psychiatric symptoms in vitamin B12 deficiency, it is likely that nitrous oxide use in this group	Thank you for your comment. If pregnant and breastfeeding women show signs or symptoms of vitamin B12 deficiency then they will be covered by this guideline and offered suitable treatment. The use nitrous oxide is not covered by this guideline. However, its interference with the action of vitamin B12 is noted in the BNF.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			could significantly increase the risk of postnatal depression and postpartum psychosis.	
Pernicious Anaemia/B12 Deficiency Support Group	004	021	Monitoring of vitamin B12 deficiency is mentioned – we would like to see this adjusted to reflect the impact on patients, e.g. quality of life measures/symptom scores. It would also be helpful to consider long term complications, e.g. cardiovascular events, serious mental illness (major self-harm, suicide, psychosis, dementia, inpatient psychiatric treatment) and long-term disability.	Thank you for your comment. The aim of this review is to look at the frequency and content of follow up. This will include the impact on quality of life and other outcomes such as complications which will be agreed by the committee when they set the protocol. We have changed the word 'monitoring' to 'follow up' to reflect this.
Pernicious Anaemia/B12 Deficiency Support Group	005	001	The vast majority of our members do not manage well on the standard 2-3 month injection frequency and the most effective and safe treatment for their symptoms is more frequent injections. Management of patient symptoms by ensuring they are prescribed frequent enough injections to relieve their symptoms is the top priority for our members. Other treatment options for management of symptoms do not need to be covered here.	Thank you for your comment. The guideline will investigate treatment of the vitamin B12 deficiency by focusing on the appropriate frequency, dose and route of vitamin B12 replacement and the impact this has on the person's quality of life.
Pernicious Anaemia/B12 Deficiency Support Group	005	004	Specific management and investigation of complications (e.g. cardiovascular events) do not need to be covered here, except to mention that providing more frequent injections will prevent or reduce the risk of complications. We would recommend stating explicitly that complications related to B12 deficiency are an indication that the patient has been under-treated and should be reviewed to ensure injection frequency is sufficient to prevent symptom breakthrough.	Thank you for your comment. The guideline will investigate treatment of the vitamin B12 deficiency by focusing on the appropriate frequency, dose and route of vitamin B12 replacement and the impact this has on the person's quality of life. Complications will only be considered as an outcome in the treatment reviews.
Pernicious Anaemia/B12	005	022	We would like to include the Women's Health Strategy here once available, as vitamin B12 deficiency has a higher	Thank you for your comment. Thank you for drawing our attention to the Women's Health strategy. We only include

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
Deficiency Support Group			incidence in women than men. This came up in the recent parliamentary debate regarding the declassification of injectable vitamin B12 from a prescription only medicine to being available over the counter, and many of our members responded to the call for evidence as a result.	NICE guidance in this section and as this is a government initiative we would not include it in this list. . We have noted in the Equality Impact Assessment for this guideline that autoimmune conditions are more prevalent in women, the symptoms are often non-specific, and women with these conditions often report having difficulty in the way their symptoms are heard, understood and treated.
Pernicious Anaemia/B12 Deficiency Support Group	006	028	Vitamin B12 deficiency causes non-alcoholic fatty liver disease and abnormal liver function tests are therefore also common.	Thank you for your comment. The review questions are draft and will be more clearly defined when the review protocols are set. Specific signs/symptoms/risk factors/comorbidities to be investigated will be agreed by the committee and pre-specified in the review protocols. The committee will consider these for inclusion in the protocol.
Pernicious Anaemia/B12 Deficiency Support Group	007	001	Given the difficulties with the various blood tests available, the potential for serious deterioration if treatment is delayed and the excellent safety profile of B12 injections, it may be more cost effective, quicker and practical to consider a therapeutic trial of injections as a diagnostic tool.	Thank you for your comment. The committee will consider including a therapeutic trial of injections as a diagnostic tool when they set the protocol for the review question. Making a recommendation in a NICE guideline for a diagnostic technique that is not current practice requires good quality evidence with objective outcomes. If the review does not find such evidence, the committee can consider making a research recommendation, but it is unlikely it will be able to justify a practice recommendation for a therapeutic trial of injections as a diagnostic tool..
Pernicious Anaemia/B12 Deficiency Support Group	007	023	It is important to consider the long term effect on symptoms, quality of life and risk of complications here, not just short term blood results.	Thank you for your comment. When setting the review protocol, the committee will agree appropriate time points for outcome measures. Outcomes will be extracted at these time points from the studies where reported.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
Royal College of Nursing	Comments Form Questions	Question 1	*Are there any cost saving interventions or examples of innovative approaches that should be considered for inclusion in this guideline?* RCN response: There are potential opportunities to build int public health agenda (in relation to lifestyle, diet etc).	Thank you for your comment. This guideline will focus on the diagnosis and management of vitamin B12 deficiency. Where appropriate it will also link to relevant NICE guidance related to lifestyle and diet.
Royal College of Nursing	Comments Form Questions	Question 2	*Do you agree to the proposed title change to "Vitamin B12 deficiency, including pernicious anaemia: diagnosis and management? Please give reasons for your answer.* RCN response: Yes, clearer title and simple language which is relevant to patients and includes pernicious anaemia.	Thank you for comment. Several stakeholders commented on the content and title of the guideline and the consensus is that it should cover all forms of vitamin B12 deficiency. We have now changed the title to "Vitamin B12 deficiency, including pernicious anaemia: diagnosis and management".
Royal College of Paediatrics and Child Health	Comments Form Questions	Question 2	The reviewer agrees with the change in name. Vitamin b12 deficiency is better than pernicious anaemia. The latter being just one cause of b12 deficiency.	Thank you for comment. Several stakeholders commented on the content and title of the guideline and the consensus is that it should cover all forms of vitamin B12 deficiency. We have now changed the title to "Vitamin B12 deficiency, including pernicious anaemia: diagnosis and management".
Royal College of Paediatrics and Child Health	General	General	The scope only touches briefly on risk factors. Veganism is a known risk factor and veganism is increasingly popular, particularly among young adults. Hence, children may also show a similar trend. They should all be offered testing and/or be educated on b12 supplementation to prevent a deficiency developing.	Thank you for your comment. The review questions listed in the scope are draft and will be more clearly defined when the review protocols are set. Specific risk factors to be investigated will be agreed by the committee and pre-specified in the review protocols. We will make the committee aware of your comment.
Royal College of Paediatrics and Child Health	General	General	There can be a risk to the foetus/neonate, if obstetric bloods suggest b12 deficiency (e.g., macrocytic anaemia) then should the mother be tested for b12 deficiency, due to the potential impact on the developing foetal nervous system. Similarly, in mothers who are b12 deficient and breast	Thank you for your comment. Identifying people at risk of vitamin B12 deficiency is covered by the scope as is treating all people diagnosed with a vitamin B12 deficiency. Pregnant women and breastfeeding mothers diagnosed with a vitamin B12 deficiency will be covered by in this guideline.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			feeding, then education on the risk to the newborn/infant nervous system from b12 deficiency should be given.	Evidence from our reviews and the review on information and support for people with a vitamin B12 deficiency will also inform the patient information recommendations.
Siemens Healthineers	004	013	Diagnosis should consider Active B12 which is now available from most of the major IVD manufacturers including Siemen Healthineers assay licensed from Axis Shield	Thank you for your comment. Diagnostic tests to be included in the evidence review will be agreed by the committee when the review protocol is set. This will include Active B12.
Siemens Healthineers	005	008	Antenatal guidelines do not seem aligned with BSH guidance on the use of Active B12 and not Total B12 to assess Vitamin B12 status in pregnancy	Thank you for your comment. This guideline will look at the evidence for diagnosing vitamin B12 deficiency and this will include looking at active and total B12 in people suspected of vitamin B12 deficiency. This will include pregnant women and the committee will base their recommendations on this evidence review.
Siemens Healthineers	005	017	Medtech report is out of date given that most major IVD manufacturers now offer Active B12 assays	Thank you for your comment. The Medtech report will be updated by this guideline.
Siemens Healthineers	005	020	Comment as above	Thank you for your comment. The Medtech report will be updated by this guideline.
Siemens Healthineers	007	002	**Total B12 test can give False Negatives due to assay interference, as seen in the following articles:** • Failures of Cobalamin assays in Pernicious Anemia Carmel and Agrawal, NEJM 2012 367;4 • Spurious Elevations of Vitamin B12 with Pernicious Anemia Yang and Cook, NEJM 2012 366;18 • Falsely elevated cobalamin concentration in multiple assays in a patient with pernicious	Thank you for providing the references. We will check these for inclusion against our protocol when we do the review. All evidence that meets the agreed review protocol will be reviewed by the committee in order to make recommendations.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			anemia: A case study van Rossum et al CCLM 2013 14:1-3 – Failure observed in Total B12 assays from Abbott, Roche, Siemens and Beckman Coulter – Pernicious anaemia patient with severe Vitamin B12 deficiency gave results well above the normal reference range	
The B12 Society	001	014 - 017	Other important causes that should be included are: drug induced deficiency which, from our 33 thousand+ members of our support group, appears to play the biggest role in vitamin B12 deficiency. This is acknowledged by NHS/drug manufacturers **on information on the side effects of certain prescription medications e.g. Metformin, PPI's etc.** **Also inborn errors such as transcobalamin II deficiency, or lack of haptocorin.**	Thank you for your comment. We have revised the introduction and made it more general to all vitamin B12 deficiency.
The B12 Society	001	018 - 019	The vast majority of our membership who have been diagnosed with B12 deficiency have had negative pernicious anaemia tests and include suitable animal products in their diets. Therefore, we question if there is research on this and who is the author? It is also noted that the previous draft states "commonest cause of B12 **anaemia**" not "most common cause of B12	Thank you for your comment. We have revised the introduction, made it more general to all vitamin B12 deficiency and removed the line stating that pernicious anaemia is the most common cause of B12 deficiency.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			deficiency". These two stats (B12 anaemia and B12 deficiency) should not be confused.	
The B12 Society	001	023 - 024	This paragraph implies that macrocytosis is the primary symptom, with neurological symptoms being "complications". This is inaccurate, as many people with B12 deficiency experience neurological issues as their first or only symptoms. It is important to clarify this, as many doctors still think that if there is no macrocytosis then there is no problem causing many B12 deficient patients to slip through the net. Low iron or normal folate will mask macrocytosis. Perhaps a better statement would be: "Vitamin B12 deficiency **CAN** cause…." And should include "neurological symptoms will regularly precede blood manifestations of deficiency"	Thank you for your comment. We have revised the introduction, made it more general and removed reference to macrocytosis.
The B12 Society	002	010 - 011	Too much emphasis on macrocytosis. This is not always the case, many do not have an MCV that is elevated above range. Full blood count can look normal with a B12 deficiency.	Thank you for your comment. We have amended the emphasis in this paragraph to state that testing for vitamin B12 deficiency is "is also part of work up of anaemia, macrocytosis and any neuro psychiatric or neuro degenerative symptoms or signs".
The B12 Society	002	011 - 013	Access to this test is virtually non-existent as are the other possible tests/indicators such as active B12 (holotranscobalamin) and homocysteine. Even when the methylmalonic acid (MMA) test is carried out, like the other tests for B12 deficiency, it is not a gold standard test, nor is it always carried out to best possible standard, e.g. urinary	Thank you for your comment. The guideline scope covers diagnosing vitamin B12 deficiency. Within this key area of the scope evidence for the diagnostic accuracy and clinical and cost-effectiveness of tests will be reviewed, and recommendations will be made where possible. Clinical effectiveness will be assessed in the context of pre-specified,

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			MMA is more accurately measured from a 24 hour sample as opposed to a single morning sample.	patient focussed outcomes, which the committee will agree upon when setting the review protocols.
The B12 Society	002	014 - 016	Although it is important to establish the cause of a B12 deficiency, we must not put too much focus on the cause since the treatment is the same initially. All causes of deficiency should be treated with B12 injections initially to ensure a as speedy a return to sufficient/efficient levels of B12 as possible. Then, and only then, if there is a clear dietary deficiency should the patient be given oral supplements	Thank you for your comment. The guideline scope covers identifying the cause of vitamin B12 deficiency. Within this key area of the scope evidence for the diagnostic accuracy and clinical and cost-effectiveness of tests will be reviewed, and recommendations will be made where possible. Clinical effectiveness will be assessed in the context of pre-specified, patient focussed outcomes, which the committee will agree upon when setting the review protocols.
The B12 Society	002	018 - 021	This statement is very worrying as the treatment should be the same regardless of the cause, and pernicious anaemia is not the only cause of malabsorption. Granted it might be that those with an absorption issue due to infection/gut dysbiosis/diet may not need injections for life.	Thank you for your comment. We have revised this statement.
The B12 Society	002	023 - 025	This is a concerning statement because any cause of b12 deficiency can lead to neurological complications, not just pernicious anaemia.	Thank you for your comment. We have revised this sentence to reflect that it relates to any vitamin B12 deficiency and that it is any complications.
The B12 Society	004	011 - 012	This should include medications known to cause/contribute to a B12 deficiency, such as metformin, proton pump inhibitors, antibiotics, antihistamines etc.	Thank you for your comment. Medications that can increase the risk of developing vitamin B12 deficiency will be considered by the committee as part of the review protocol for this question.
The B12 Society	004	015 - 017	Intrinsic factor negative Pernicious Anaemia and Drug induced deficiency must be considered during this process.	Thank you for your comment. The tests to be included in the evidence review will be agreed by the committee when the review protocol is set. All forms of vitamin B12 deficiency will be included in the review.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			However trying to determine the cause should not delay/preclude treating the deficiency. There must be far more awareness that testing **once on** injections or supplements will not be an accurate reflection of what their patients have at a cellular level.	The committee will consider your points about not delaying treatment once diagnosed and the impact of vitamin B12 replacement on testing.
The B12 Society	004	018	Must include treatment with appropriate cofactors where necessary to achieve optimal recovery, e.g. folic acid/folate, iron, vitamin B6	Thank you for your comment. The guideline will focus on treating the vitamin B12 deficiency rather than the cofactors.
The B12 Society	004	020	This should not include the retesting of serum B12 levels	Thank you for your comment. The committee will consider whether to include retesting of serum B12 levels as part of the review on monitoring when it sets the protocol.
The B12 Society	004	031	Mothers known to be deficient should have their babies screened for low b12 as this can be a main cause for babies born low.	Thank you for your comment. This will be considered by the committee when setting the review question on risk factors for vitamin B12 deficiency.
The B12 Society	005	001 - 002	Provided this guideline gives clear unambiguous guidance, then the appropriate B12 treatment along with the essential cofactors will ensure the patient's symptoms are managed effectively	Thank you for your comment. The guideline will focus on treating the vitamin B12 deficiency rather than the cofactors.
The B12 Society	005	006 - 007	NICE guideline on "Anaemia - B12 and folate deficiency" should be included.	Thank you for your comment. NICE does not currently have a guideline on Anaemia - B12 and folate deficiency. There is a Clinical Knowledge Summary (CKS) on NICE's website https://cks.nice.org.uk/topics/anaemia-b12-folate-deficiency/ but this is not a guideline. These summaries are usually updated to reflect NICE guidelines once they are published.
The B12 Society	005	019	NICE guideline on "Anaemia - B12 and folate deficiency" should be included.	Thank you for your comment. NICE does not currently have a guideline on Anaemia - B12 and folate deficiency. There is a Clinical Knowledge Summary (CKS) on NICE's website

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
				https://cks.nice.org.uk/topics/anaemia-b12-folate-deficiency/ but this is not a guideline. These summaries are usually updated to reflect NICE guidelines once they are published.
The B12 Society	006	006 - 013	Early diagnosis with appropriate treatment will save much time for doctors appointments, unnecessary referrals to consultants, prescriptions, and nurse time (allow patients to self-administer at home). For Pernicious Anaemia and other malabsorption causes of deficiency tablets do not help, only hydroxocobalamin injections. The only group who may see an improvement with oral supplementation is where diet is poor/deficient but they still improve far quicker with injections.	Thank you for your comment. These points will be considered when prioritising areas for economic modelling, and for inclusion in any model in the guideline.
The B12 Society	006	019 – 021	Dietary advice on foods that contain vitamin B12 should be given, including information on potentially harmful analogue forms of B12 that are contained in foods such as spirulina and some fortified foods. This can also be the case with some supplements, often labelled as "vegan friendly". These analogue forms can do more harm to those already deficient in B12 as they block absorption channels. This should be given at the outset of diagnosis	Thank you for your comment. The guideline will include recommendations on what information to give people with vitamin B12 deficiency based on a review of the qualitative literature and the committee experience.
The B12 Society	006	022 - 025	Advice should be given to inform that there are currently no gold standard tests for B12 deficiency, and that Intrinsic Factor Antibody & Anti-Parietal Cell Antibody tests are not always conclusive. This should be given at the testing stage.	Thank you for your comment. The guideline will include recommendations on what information to give people with vitamin B12 deficiency based on a review of the qualitative literature and the committee experience.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			Once diagnosed they should be advised that treatment by injection (Intramuscular or subcutaneous) should be life long, unless the absorption issues can be resolved, like in cases such as parasitic infections if the cause/damage can be reversed. This should be at the diagnosis stage. If Pernicious Anaemia is confirmed, the patient/family/carers should be advised that it is a recognised autoimmune disease.	
The B12 Society	006	028 - 030	All of these factors should play a part in considering B12 deficiency as a cause of patients health issues, with signs & symptoms playing the lead role, followed by blood manifestations, risk factors, then comorbidities.	Thank you for comment. This is the aim of this question and the committee will be able to make recommendations in these areas based on the evidence found in this review.
The B12 Society	007	006 - 009	A trial of injections for a positive clinical response is the most accurate diagnosis as there is no gold standard test and b12 is not a placebo.	Thank you for your comment. The committee will consider including a therapeutic trial of injections as a diagnostic tool when they set the protocol for the review question. Making a recommendation in a NICE guideline for a diagnostic technique that is not current practice requires good quality evidence with objective outcomes. If the review does not find such evidence, the committee can consider making a research recommendation, but it is unlikely it will be able to justify a practice recommendation for a therapeutic trial of injections as a diagnostic tool.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
The B12 Society	007	012 - 016	There is no god standard test for vitamin B12 deficiency including pernicious anaemia, so tests that fall within reference ranges do not exclude a B12 deficiency. Added to this, many people try supplements that contain vitamin B12 prior to being tested for their levels, so there is a high potential for results to be skewed, and a false high is enough to make most health professionals deem there to be no deficiency in the patient. Therefore it is essential that health professionals are aware of this, and allowances made for such potential when assessing test results.	Thank you for your comment. The committee will consider this when setting the protocols and reviewing the evidence.
The B12 Society	007	023 - 025	Frequency of injection must be determined by the patients symptoms and not their test results	Thank you for your comment. The committee will review the evidence in this area and then make recommendations accordingly.
The B12 Society	008	003 - 004	Patients cofactor levels should be tested, these should include folate, ferritin, vitamin B6, potassium as standard, with added tests such as thyroid, vitamin D etc if symptoms suggest necessary. Monitoring could also include a patient symptom log to help track changes Monitoring should NOT include testing serum B12 levels!	Thank you for your comment. The committee decide on the detail to include in the protocol, review the evidence in this area and then make recommendations accordingly. Testing for cofactors is outside the remit of this guideline. The committee will decide whether to review the evidence for a patient symptom log or testing for B12 at follow up is a priority for this guideline.
The B12 Society	008	015	Is this in reference to patient or physician? We are currently seeing a spike in patients being told that a new guideline has been issued stating that patients (including those with	Thank you for your comment. This is in reference to adherence to treatment by person receiving it.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			confirmed PA) are to be given oral supplements instead of injections. HGH - Total clarity of both diagnosis and management of B12 deficiency, including PA is essential so that neither doctors nor patients can misinterpret this guideline. It is highly likely that patients who are given B12 injections at the most effective frequency for their deficiency, along with appropriate cofactors will gratefully adhere to their treatment plan, as the benefits are all too often the difference between living life and simply existing.	This guideline will review the evidence on diagnosis and management for all vitamin B12 deficiency and make recommendations or recommendations for research where possible. It will include looking at the dose, frequency and route of delivery that will incorporate comparing oral supplements and injections.
The B12 Society	General	General	HGH - The following should be added somewhere. * taking supplements containing b12 prior to b12 tests will mask an underlying deficiency. * do not retest b12 once treatment has begun. *monitoring of co factors is very important during b12 treatment (folate, potassium and iron)	Thank you for your comment. These points will be considered by the committee when setting the protocols.
The B12 Society	General	General	There are too many of us diagnosed as B12 deficiency with Intrinsic Factor & Anti Parietal Cell Antibody negative, but with debilitating symptoms and life-threatening complications just as in PA patients, therefore it is essential that all deficiencies of any cause are treated with the same	Thank you for your comment. We are aware that there are a diverse range of causes for vitamin B12 deficiency and agree that each should be treated with equal respect. The guideline reviews will be stratified by the cause of vitamin B12

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			respect as they would be if it were PA. Currently this almost dismissive approach to non-PA deficient patients is creating unnecessary suffering to many patients across the UK. The financial cost of which must be astronomic to the NHS!	deficiency to ensure that different recommendations can be made for each cause where evidence permits.
The B12 Society	General	General	Total clarity of both diagnosis and management of B12 deficiency, including PA is essential so that neither doctors nor patients can misinterpret this guideline.	Thank you for your comment. The guideline aims to provide a clear set of recommendations for diagnosis and management.
The B12 Society	General	General	Current reference ranges are heavily unreliable with each health board setting their own that can range anywhere between 110ng/L to 230ng/L at the bottom of range. This creates unacceptable inconsistency.	Thank you for your comment. The committee will discuss the reference ranges to use when setting the protocols for the review questions. Reference ranges of diagnostic tests will be reported in the evidence reviews where available from the studies. This will allow the committee to make recommendations on reference ranges where there is sufficient evidence.
The Breastfeeding Network	003	021	The scope mentions that specific consideration will be given to pregnant women with a vitamin B12 deficiency including pernicious anaemia. We feel that this should include breastfeeding women as well. A vitamin B12 deficiency in a breastfeeding mother can lead to a deficiency in her child. This is a particular risk for mothers following a strict vegetarian or vegan diet. However, this can be avoided with appropriate dietary management and treatment for the mother, to ensure adequate B12 levels in her breastmilk. (Dror DK, Allen LH. Vitamin B-12 in Human Milk: A Systematic Review. Adv Nutr. 2018 May 1;9(suppl_1):358S-366S.) Maternal vitamin B12 supplementation is safe for breastfeeding children	Thank you for your comment. Identifying people at risk of vitamin B12 deficiency is covered by the scope as is treating all people diagnosed with a vitamin B12 deficiency. Breastfeeding is also included in the NICE guideline on Maternal and child nutrition which is currently being updated and therefore has not been included as a special consideration here. However, breastfeeding mothers diagnosed with a vitamin B12 deficiency will be covered by this guideline.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			(https://www.nhs.uk/medicines/cyanocobalamin/). Breastfeeding has substantial health benefits for both mother and child, and should be protected when discussing diet and B12 deficiency, management and treatment with a pregnant or breastfeeding mother.	
The Breastfeeding Network	Comments Form Questions	Question 3	In response to question 3, above, we would suggest that the guideline specifically address the importance of identifying pregnant and breastfeeding mothers at risk of B12 deficiency and protecting and encouraging breastfeeding in these mothers. A vitamin B12 deficiency in a breastfeeding mother can lead to a deficiency in her child. This is a particular risk for mothers following a strict vegetarian or vegan diet. However, this can be avoided with appropriate dietary management and treatment for the mother, to ensure adequate B12 levels in her breastmilk. (Dror DK, Allen LH. Vitamin B-12 in Human Milk: A Systematic Review. Adv Nutr. 2018 May 1;9(suppl_1):358S-366S.) Maternal vitamin B12 supplementation is safe for breastfeeding children (https://www.nhs.uk/medicines/cyanocobalamin/). Breastfeeding has substantial health benefits for both mother and child, and should be protected when discussing	Thank you for your comment. Identifying people at risk of vitamin B12 deficiency is covered by the scope as is treating all people diagnosed with a vitamin B12 deficiency. Breastfeeding is also included in the NICE guideline on Maternal and child nutrition which is currently being updated and therefore has not been included as a special consideration here. However, breastfeeding mothers diagnosed with a vitamin B12 deficiency will be covered in this guideline.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21

Stakeholder	Page no.	Line no.	Comments	Developer's response
			diet and B12 deficiency, management and treatment with a pregnant or breastfeeding mother.	
Viapath	001	019	The estimate of deficiency used in this document appears low. The text doesn't cite references where this figure was taken from.	Thank you for your comment. We have updated the figures.
Viapath	001	023	The way the text is written has too much of an emphasis on the haematological symptoms and may infer to the reader that expressing a haematological deficit is the initial finding – followed by neurological symptoms if the B_{12} deficiency is left untreated. This is not the case. Different patients present in different ways and some B_{12} deficient patients have a clear neurological deficit but no haematological symptoms.	Thank you for your comment. We have revised the introduction and made it more general.
Viapath	003	014	It is worth noting that reference ranges that help with the interpretation of laboratory tests are often derived from populations that do not represent the ethnic diversity of patient cohorts or pregnant mothers and children where the assay is performed.	Thank you for your comment. The committee will consider appropriate reference ranges and ethnicity when setting the protocols for the review questions. Where appropriate reviews will be stratified by different ethnic groups to take into account these differences.
Viapath	General	General	Fully supportive of the proposed new title. The initially proposed title would have excluded many patients with vitamin B_{12} deficient states – pleased to see other causes of vitamin B12 deifciency presented in Section 1.	Thank you for comment. Several stakeholders commented on the content and title of the guideline and the consensus is that it should cover all forms of vitamin B12 deficiency. We have now changed the title to "Vitamin B12 deficiency, including pernicious anaemia: diagnosis and management".
Viapath	General	General	The convention is to write vitamin B_{12} with a subscript	Thank you for your comment. The NICE style is to include it all in normal text and it is also consistent with the NHS style.

Pernicious anaemia

Consultation on draft scope
Stakeholder comments table

08/09/21 to 06/10/21