NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

Contents:

The following documents are made available to consultees and commentators:

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

2. **Comments on the Appraisal Consultation Document from Roche Products**
   a. ACD comments form
   b. ACD comments appendix

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Spinal Muscular Atrophy UK-Muscular Dystrophy UK
   b. TreatSMA
   c. SMA Reach UK
   d. SMA Reach UK

4. **Comments on the Appraisal Consultation Document from experts:**
   a. Anne-Marie Childs – clinical expert, nominated by Muscular Dystrophy UK and Roche Products

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

6. **Evidence Review Group critique of company comments on the ACD**

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

Appraisal title

Single Technology Appraisal

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

Type of stakeholder:

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

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

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

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

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

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	Roche	**Introduction** Roche appreciates the opportunity to provide comments on the NICE Appraisal Consultation Document (ACD) for risdiplam for treating spinal muscular atrophy (SMA) [ID1631]. Roche is dedicated to finding solutions in collaboration with NICE for the concerns raised within the ACD such that risdiplam may be considered for a positive recommendation for use within the NHS. Despite existing treatment options, the unmet need remains high in this highly disabling disease area for a treatment that is able to: • Delay disease progression and maintain patients' existing motor abilities so they can continue to live their normal daily lives; • Improve or maintain essential bodily functions including the ability to breathe (respiratory function), swallow, vocalise and verbally communicate, as well as delay or prevent significant damage to the spine (scoliosis); • Increase patient survival such that they are able to spend more time with family, friends and loved ones. Moreover, this unmet need is further illustrated by the ongoing risdiplam Early Access to Medicines Scheme, in which over 200 patients have been enrolled so far. Rationale is provided in the comments below for instances where Roche would like to encourage the Committee to reconsider its conclusions. Roche has also submitted an appendix containing additional cost-effectiveness data to provide further support for the model assumptions. This response covers the following key points, addressing the concerns raised in the ACD: • Long-term follow-up from the SUNFISH and FIREFISH trials (24-month data) • Risdiplam treatment in pre-symptomatic patients and previously treated patients • Revised discontinuation criteria for risdiplam	Thank you for your comments. The appraisal committee considered the company's new evidence and updated cost-effectiveness results at the second meeting. Risdiplam will be made available through a managed access agreement (MAA). Access to risdiplam will be defined within the terms of the MAA. The committee agreed that risdiplam was promising and the substantial uncertainty discussed as part of this appraisal would be addressed by a full review after the

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			• Upper limb function utility for patients and carers • Alternative approach to modelling carer disutility • Bulbar function, respiratory and scoliosis patient disutilities and costs The revisions outlined below change the incremental cost-effectiveness ratio (ICERs) to £[redacted] for type 2/3 SMA and between £[redacted] and £[redacted] for type 1 SMA. Roche acknowledges that a range of ICERs are not usually presented in the base-case, however modelling approaches face particular challenges in type 1 SMA, such as the effect of the extension to life achieved with risdiplam on carer quality-adjusted life years (QALYs), which Roche has attempted to address below. Additionally, challenges are posed through SMA being a highly expensive disease to treat, which requires care from multiple healthcare professionals and specialist equipment. Roche would like to highlight that whilst increasing survival does increase patient life years, it also increases costs and carer QALY losses, which are detrimental to the ICER of risdiplam In addition, Roche requests that the decision-modifiers taken into account for the appraisal of nusinersen are also applied for risdiplam, given the rarity and highly disabling nature of the disease, the high mortality of people with SMA, many of whom are children, as well as the severe disease burden, which has wider societal impacts in terms of emotional and financial effects on people with SMA and their families. As noted above, Roche feels strongly that risdiplam can address a significant unmet need for an effective treatment for SMA patients in the UK, and wishes to note that the ICERs presented herein - following the revisions requested by the committee and inclusion of longer-term clinical data - are substantially lower than those reviewed at the first Appraisal Committee Meeting. Roche is committed to enabling people with SMA to gain access to risdiplam and is open and willing to continue collaboration as needed with NICE and NHS England to enable this to happen.	MAA period has finished.
2	Company	Roche UK	**Long-term follow-up from the SUNFISH and FIREFISH trials (24-months data)** Additional clinical data from the 24-month data cut of the trials investigating the effect of risdiplam on type 2/3 (SUNFISH trial) and type 1 (FIREFISH trial) SMA patients has become available since the original company submission. Results from the 24-month data cut of the SUNFISH trial demonstrate the continued efficacy of risdiplam, with further improvements in key endpoints recorded in comparison to the 12-month data, which informed the original company submission. Specifically, the following clinical results were obtained at the 24-month data time point:[1] • The mean change in 32-item Motor Function Measure (MFM-32) total score from baseline increased from 1.65 at 12 months to 1.83 at 24 months. • The upper limb function measured by the mean change in the Revised Upper Limb Module	The committee considered these data at the second meeting.

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			(RULM) total score further improved from 1.91 at 12 months to 2.79 at 24 months. • The mean change in the Expanded Hammersmith Functional Motor Scale – Expanded (HFMSE) total score also improved from 1.81 at 12 months to 2.15 at 24 months. • The patient-reported SMA Independence Scale (SMAIS) mean change was maintained at a similar score from baseline (0.95 at 12 months, 0.82 at 24 months), while the mean change in carer-reported SMAIS scores from baseline improved from 1.68 at 12 months to 2.73 at 24 months. These data demonstrate that risdiplam continues to have a beneficial impact on patients' motor abilities (as shown through MFM-32 and HFMSE scores) in addition to upper limb function (as demonstrated by the RULM scores). As supported by the SMAIS scores, these improvements enable patients to maintain their independence and quality of life (QoL). The 24-month data have been incorporated into the type 2/3 model so that it is informed by longer-term efficacy data for risdiplam. The FIREFISH 24-month data also demonstrate the continued efficacy of risdiplam in comparison to the 12-month data cut. Specifically, the following clinical results were obtained at the 24-months data time point:[2] • The proportion of patients sitting without support for 5 seconds (using the Bayley Scales of Infant and Toddler Development, Third edition [BSID-III] measure) increased from 29% (at 12 months) to 61% (at 24 months). • The proportion of patients who achieved a score of 40 or higher in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) increased from 56% (at 12 months) to 76% (at 24 months). • Similarly, the proportion of motor milestone responders as assessed by the Hammersmith Infant Neurological Examination, Module 2 (HINE-2) measure increased from 78% (at 12 months) to 85% (at 24 months). The proportion of patients able to support their weight or stand with support, as assessed by HINE-2, increased from 22% to 27% from 12 months to 24 months. While assessing the walking item of HINE-2, the proportion of patients that were able to bounce were also recorded, and this increased from 2% at month 12 to 4% at month 24. • The proportion of patients alive (across with and without permanent ventilation) remained high at 83% at 24 months. • The proportion of patients that were able to feed orally was maintained at a high level (83% at month 12 and 85% at month 24). These data demonstrate that risdiplam continues to have a beneficial impact on the motor abilities of type 1 SMA patients (as shown through BSID-III, CHOP-INTEND and HINE-2 scores). As noted by the Committee in the ACD, type 1 SMA patients on BSC typically die within 2 years if they do not receive respiratory support.[3] In FIREFISH, 83% of patients that do not receive permanent ventilation were alive at the 24-month data cut. Therefore, risdiplam extends life for type 1 SMA patients, as well as enabling	

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			them to maintain or improve their QoL, through improved motor function and the ability to feed orally. The 24-month data have been incorporated into the type 1 model so that it is informed by longer-term efficacy data for risdiplam.	
3	Company	Roche UK	**<u>Risdiplam treatment in pre-symptomatic patients</u>** ***RAINBOWFISH clinical evidence*** The open-label Phase II study (RAINBOWFISH, NCT03779334[4]), investigating the efficacy and safety of risdiplam in infants with genetically diagnosed and presymptomatic SMA is currently recruiting. Preliminary data were presented at the Cure SMA Virtual Research & Clinical Care Meeting (June 7–11, 2021).[5] RAINBOWFISH (NCT03779334) is a multicentre, open-label, single-arm, study to investigate efficacy, safety and pharmacokinetics (PK)/pharmacodynamics (PD) of risdiplam in infants with genetically diagnosed presymptomatic SMA. RAINBOWFISH is actively enrolling infants aged from birth to 6 weeks (at first dose), regardless of *SMN2* copy number. Infants will receive risdiplam for 24 months, followed by a 36-month extension. Primary analyses will be conducted at 12 months of treatment in infants with two *SMN2* copies and compound muscle action potential (CMAP) amplitude ≥1.5 mV at baseline. The primary endpoint is the proportion of these infants sitting without support for ≥5 seconds after 12 months of treatment (assessed by Item 22 of the Gross Motor Scale of the Bayley Scales of Infant and Toddler Development, Third Edition). Secondary endpoints include the development of clinically manifested SMA, survival and permanent ventilation, achievement of motor milestones, motor function, growth measures, nutritional status, CMAP, PK and safety monitoring. For the first 12 enrolled infants, the median age at first dose was 28.5 days (range: 16–40 days). SMN protein data are currently available for nine of these infants. The mean baseline SMN protein level in blood prior to risdiplam treatment was 5.8 ng/mL, which was higher than the mean baseline SMN protein levels in patients in the FIREFISH (type 1 SMA patients; 2.7 ng/mL) and SUNFISH (type 2/3 SMA patients, 3.4 ng/mL) studies of risdiplam. Enrolled infants have been treated with risdiplam for a median of 7.4 months (range: 1.1–18.1 months). Five infants have been treated for ≥12 months (preliminary efficacy data are available for these infants) and includes two infants with two *SMN2* copies and three infants with >2 *SMN2* copies. Three infants have been treated for ≥6 to <12 months, and five infants treated for <6 months. Infants treated with risdiplam for at least 12 months (n=5) reached near maximum CHOP-INTEND scores by 4–5 months of age. At 4 months of treatment, 4/5 infants (80%) scored ≥60, 1/5 infants (20%) scored 58. At 12 months of treatment, 5/5 infants (100%) scored ≥60; 4/5 infants (80%) scored the maximum CHOP-INTEND score of 64 (including both infants with two *SMN2* copies), with the remaining 1/5 infant (20%) scoring 63 with a subsequent score of 64. Infants treated with risdiplam for at least 12 months (n=5) achieved Hammersmith Infant Neurological Examination, Section 2 (HINE-2) motor milestones; at the 20th February 2021 data cut-off, 80% of infants	The committee considered these data at the second meeting.

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			(4/5) scored the maximum HINE-2 score of 26; this includes one infant with two *SMN2* copies, one infant with two *SMN2* copies had a HINE-2 total score of 23. This means that head control, sitting, rolling, and crawling milestones were achieved in all five babies; four (80%) were able to stand unaided and walk independently, with one baby standing with support and one bouncing. Most of the infants treated for at least 12 months achieved motor milestones within the World Health Organisation Multicentre Growth Reference study group (WHOGRS) windows for healthy children. No treatment-related serious adverse events were reported in pre-symptomatic infants treated with risdiplam for up to 18.1 months; adverse events were more reflective of the age of the infants rather than the underlying SMA (nasal congestion reported in four babies (33%), cough, teething and vomiting reported in three babies (25%), and two babies each reporting eczema, abdominal pain, diarrhoea, gastroenteritis, papulae and pyrexia (17%)). When this is compared with the natural history of type 1 SMA, these data are remarkable. The ANCHOVY study was a global, multicentre, chart review study that provided an update on natural history data in patients with type 1 SMA from a broad geographical area[6]. Patient data (n=60) were extracted from medical records from sites in Belgium (n=5), Brazil (n=6), Croatia (n=3), France (n=10), Italy (n=10), Japan (n=7), Poland (n=4), Russia (n=8) and the USA (n=7). Thirty cases (50%) had confirmed *SMN2* copy number (the remaining 30 (50%) patients the *SMN2* copy number was unknown). Among the patients who had data, no patients achieved any level of sitting or head control after 9 months of age. One patient (two *SMN2* copies) was able to sit with support at 9 months of age, eight patients achieved the head control item “wobbles” (four patients had two copies of *SMN2*, four patients had unknown *SMN2* copies) at some time up to 9 months of age, one patient (unknown *SMN2* copies) was able to maintain upright head control at 6 months of age. No patients were able to sit without support. By 12 months of age, no HINE-2 motor milestones were achieved for rolling, voluntary grasp and kicking, and no patients achieved any level of crawling, standing or walking. These results illustrate clear and clinically meaningful improvements of risdiplam-treated patients in the RAINBOWFISH study compared to SMA patients observed in the ANCHOVY study. Roche therefore request that the Committee considers this evidence in their decision-making for use of risdiplam in pre-symptomatic SMA patients.	
4	Company	Roche UK	**Risdiplam treatment in previously treated patients** ***JEWELFISH clinical evidence*** There is a growing body of evidence to support the use of risdiplam in people who have previously received alternative SMA therapy. JEWELFISH (NCT03032172) is a multi-centre, exploratory, non-comparative, open-label study investigating the safety, tolerability, PK and PK/PD relationship of risdiplam in adults, children and infants (aged 6 months to 60 years, n=174) with SMA who have previously been treated with other disease-modifying treatments.[7] The enrolled population included a broad range of ages (1–60 years), SMA types (1–3), *SMN2* copy numbers (1–4) and motor function (non-sitters, sitters and walkers). One patient withdrew from the study at baseline; of the remaining patients, 13 previously received RG7800, 76 received nusinersen (three	The committee considered these data at the second meeting.

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			patients in the nusinersen group had also received olesoxime previously), 70 received olesoxime and 14 received onasemnogene abeparvovec (AVXS-101; one patient in the onasemnogene abeparvovec group received treatment with onasemnogene abeparvovec first followed by nusinersen).[8] All patients had at least a 90-day period between the last dose of treatment and JEWELFISH screening. Risdiplam treatment led to a rapid and sustained, >2-fold increase in SMN protein levels compared with baseline levels in patients previously treated with nusinersen or onasemnogene abeparvovec[9], which was consistent with PD data from the SUNFISH study of treatment-naïve patients with Types 2/3 SMA. No drug-related safety findings leading to withdrawal were reported for any patient exposed to risdiplam in JEWELFISH. The safety profile of risdiplam was consistent with the safety profile observed in treatment-naïve patients. The JEWELFISH population is broad and heterogeneous, with a high degree of motor impairment at baseline, reflecting the real-world SMA population. Interim exploratory efficacy data demonstrated overall stabilisation in motor function at Month 12 in patients who began treatment with risdiplam following previous treatments. In a recent survey of 1474 people with SMA in Europe, >96% considered stabilisation of SMA important progress.[8] Of the 77 patients who previously received nusinersen, 24 patients (31%) reported treatment-related tolerability concerns relating to this treatment (challenges associated with intrathecal administration in patients with scoliosis or those who had undergone spinal surgery and were unable to receive a lumbar puncture); 14 patients (18%) cited lack of efficacy and eight patients (10%) loss of efficacy. Seven caregivers (9%) requested risdiplam treatment preferentially to nusinersen, and six patients (8%) cited patient preference as reason to enrol onto the JEWELFISH study. Other reasons were given in 18 cases (23%), and included treatment-related safety concerns, treatment reimbursement/insurance policy challenge, access infrastructure challenges (e.g. accessibility to hospital facilities), injection procedures, inconvenience of treatment, (or missing reason). This clearly demonstrates that some patients who have already had access to nusinersen are not able to receive continued nusinersen therapy for medical reasons. Patients in the JEWELFISH study previously treated with onasemnogene abeparvovec (n=14) cited hopes of additional benefit (n=8; 57%), caregiver preference (n=4; 29%), and treatment response (lack of efficacy, n=2; 14%) as the primary reason for enrolment into JEWELFISH. ***Experience within the risdiplam Early Access to Medicines Scheme (EAMS, MHRA EAMS Number: 00031/0011)*** Further evidence for use of risdiplam in previously treated patients is available from the Early Access to Medicines (EAMS) scheme. EAMS aims to give patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need. The risdiplam EAMS was approved for the following indication on the 17th September 2020: *Risdiplam is indicated for the treatment of patients 2 months of age and older with type 1 and type 2 spinal muscular atrophy (SMA) who are not suitable for authorised treatments.*	

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			Two hundred and three patients have been enrolled on the scheme so far, the oldest aged 69 years and the youngest less than one year of age. Type 2 patients represent the largest number of patients enrolled (n=180), with 23 type 1 patients enrolled into the scheme. Thirty patients had received previous treatment for SMA: three with olesoxime and 27 with nusinersen (two patients only received the first loading dose of nusinersen, one of these was unsuccessful); the additional patient was reported as receiving pre-treatment with salbutamol. Reasons for switching from nusinersen were documented to be scoliosis and spinal surgery impacting the ability to administer nusinersen intrathecally, despite some clinicians reporting use of general anaesthetic and interventional radiology. Adverse events and inability to tolerate nusinersen/IT administration was also recorded, with post-lumbar puncture vomiting and severe hypokalaemia reported for one patient each. One patient required tracheostomy whilst on nusinersen therapy so was unable to continue nusinersen due to the requirements of the managed access agreement. ***Clinical opinion*** Roche has consulted clinical experts (six neurologists and one physiotherapist) on whether they believe risdiplam would be effective in patients after a previous SMA therapy. Given its availability through a managed access agreement in the UK, the majority of clinical experience was based on switching from nusinersen. The clinical experts generally felt that risdiplam would be as effective as nusinersen, due to the similar mechanism of action, and that previously treated patients should therefore benefit from risdiplam.[10] One clinician mentioned that they had a few patients that switched from nusinersen to risdiplam and no health decline has been observed, and several reported improvements in bulbar and respiratory function.[10] Clinicians additionally emphasised that the oral route of administration for risdiplam is favourable.[10] In particular, clinicians have been keen to emphasise that the intrathecal administration of nusinersen is often a much more complex procedure than a typical intrathecal administration, such as for an oncology medicine. People requiring SMA therapy tend to have increasing degrees of scoliosis, which means continuous nusinersen administration over a number of years will become increasingly difficult. This raises further concern over exposure of patients to repeated X-rays/interventional radiology, and in addition, sedation (or general anaesthesia, if available in the centre) has associated risks that are exacerbated in a population that inherently has respiratory issues. In comparison, clinical experts positively commented on the oral route of administration for risdiplam, which may be administered at home, and noted that it may therefore be of interest to switch patients on nusinersen to risdiplam.[10] In the NHSE algorithm shown at the first Appraisal Committee Meeting, switching between nusinersen and risdiplam due to disease progression, patient choice, side effects, spinal access etc. was suggested as appropriate for a future patient pathway. Based on this pathway, Roche would like to ask the Committee to consider recommending risdiplam for previously treated patients, given the benefits that risdiplam would bring to this subgroup.	
5	Company	Roche UK	**<u>Revised discontinuation criteria for risdiplam</u>** Roche appreciates the criticism from the Evidence Review Group (ERG) that the time-based stopping rule submitted during technical engagement was not based on hard evidence, and understand the	The committee considered the revised

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			reasoning of the Committee that the stopping rules were not appropriate.[3] Roche has therefore included a stopping rule based on clinical criteria instead, in line with the ERG's recommendation. Based on guidance provided by the ERG on how a stopping rule may be best implemented in the models given their existing functionality, the following patient populations discontinue treatment with risdiplam at the time that they reach a 'plateau' in the updated models: • Type 2/3 SMA patients that have not reached the ability to sit unsupported [redacted % of type 2/3 patients] • Type 1 SMA patients that have not reached the ability sit [redacted % of type 1 patients]. The fact that so few risdiplam-treated patients discontinue at this timepoint reflects the high efficacy level of risdiplam and high proportions of patients in higher health states at this model timepoint. The rationale for selecting the timepoint at which patients 'plateau' is that at this timepoint no further improvement in motor milestone achievement is expected, and thus it may be assumed patients will not go on to achieve more advanced milestones in the future. NICE accepted in the ACD that a treatment-effect plateau of month 26 for type 2/3 SMA and month 66 for type 1 SMA is acceptable and consistent with NICE's technology appraisal of nusinersen.[3] Roche would like to highlight that aligning with the ERG's suggestion still reflects an outcome-based stopping rule, therefore putting considerable pressure on patients. Accordingly, Roche would like to emphasise that the discontinuation criteria are implemented in the models as a proxy for the purposes of Committee decision-making, and do not fully reflect how discontinuation criteria would be applied in clinical practice. Roche stresses that recently consulted clinicians felt strongly that the model approach should not be transferred to clinical practice.[10] If NICE chooses to impose an outcomes-based stopping rule on risdiplam, Roche requests that this aligns with the updated stopping rule for nusinersen. When deciding whether a patient should stop or continue treatment with nusinersen, the following criteria are considered by the treating clinician:[11] • Worsening of motor function • Requirement for permanent ventilation • Inability to administer the drug safely An additional stopping rule for type 3 SMA patients who lose ambulation after 12 months of treatment with nusinersen was recently removed.[11,12] Clinical experts consulted by Roche noted that the clinical guidance for risdiplam should reflect the guidance for nusinersen, as these are already established and clinicians appreciate consistency and are used to implementing them in clinical practice.[10]	discontinuation criteria. See section 3.17 of the FAD.
6	Company	Roche UK	**<u>Upper limb function utility</u>** As confirmed by patient experts during the first Appraisal Committee Meeting, the Committee noted that even small improvements in motor skills are highly valued by SMA patients, as they are important to maintain their independence, thereby making a substantial difference to the patients' QoL.[3] The Committee acknowledged during the first Appraisal Committee meeting that the SUNFISH trial showed improvements in upper limb function and SMAIS score at 12 months.[3] As mentioned above, the upper limb function measured by the mean change in RULM total score from baseline further improved from	The committee considered these analyses. See section 3.16 of the FAD.

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			1.91 at 12 months to 2.79 at 24 months.[1] Additionally, the mean change in patient-reported SMAIS was maintained at a similar score from baseline (0.95 at 12 months, 0.82 at 24 months), while the mean change in carer-reported SMAIS scores from baseline improved from 1.68 at 12 months to 2.73 at 24 months.[1] Therefore the 24-month data from SUNFISH further demonstrates the effect risdiplam has on maintaining or improving upper limb function and independence of SMA patients. In the ACD, the Committee noted that its preferred assumptions included a larger additional utility gain for fine motor skills than originally proposed by Roche at technical engagement, as some fine motor skills may not be captured in available motor function measures.[3] Roche subsequently consulted clinical and patient experts, who confirmed that the utility increase associated with upper limb function used in the technical engagement models are too low.[10] Several clinical and patient experts indicated that upper limb function improves a patient's QoL by ~50%.[10] The impact of upper limb function was emphasised by clinical and patient experts, who named the following examples of functions that patients without upper limb function would not be able to perform: ability to hold a drink and maintain hydration independently, ability to feed independently (open fridge, open bags, undo lids, chop up food, etc.), ability to move independently (access lifts, open doors, wheelchair control etc.), ability to write, control a computer mouse or a wheelchair joystick control, and the ability to scratch one's own nose.[10] One clinical expert commented that fatigue/stamina has an impact on a persons' upper limb function; he commented that nusinersen patients anecdotally refer to a decline in energy at the end of their 4-month dosing period. Continuous treatment with risdiplam should avoid this drop and personal accounts from several patients have endorsed this.[10] It is therefore clear that upper limb function has a substantial impact on patient's QoL, and as such should be accounted for in the cost-effectiveness models. Roche would like to note that, unfortunately, it is not straightforward to account for this increase in the models. Therefore, Roche has instead increased the patient utility associated with upper limb function to [redacted] in all health states where this had previously been applied during the technical engagement step (the "not sitting", "sitting with support" and "sitting without support" health states in the type 2/3 model, and the "not sitting" and "sitting" health states in the type 1 model). In addition, given the high levels of independence granted to people with SMA through upper limb function, as evidenced by feedback received from patients and carers,[10] a utility increment of 0.05 has been applied to caregivers in the risdiplam arm for the same aforementioned states in each model. As the effect that upper limb function can have on the QoL is stark according to clinical experts, patients and carers,[10] this estimate is highly likely to be conservative. Therefore, the models may still not fully reflect the clinical benefits of risdiplam. Accordingly, the company would like to request flexibility with regards to decision making.	
7	Company	Roche UK	**<u>Alternative approach to modelling carer disutility</u>** The company acknowledges the ERG's criticism that the additive approach to carer QALYs implicitly assumes that the carer either dies or survives with zero utility when the SMA patient dies, and results in the assumption that society places value on carers of surviving SMA patients but not on bereaved carers.[3] The company also agrees with the limitations of the ERG's approach to carer disutilities as	The company considered this alternative approach. See section 3.15 of the

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			highlighted by the Committee: the ICER increases as a result of subtracting substantial carer disutilities from the patient utility values, which themselves already reflect a poor QoL. As a result, the increased survival of risdiplam-treated patients results in a low number of QALYs at a high extra cost, particularly in the type 1 model. The Committee recognised the difficulties in valuing carer QoL in the ACD, noting that the "QALY loss" approach taken by the ERG has limitations, as it did not believe that including carer QoL would result in fewer carer QALYs when risdiplam extends survival of the patient.[3] Accordingly, Roche has explored alternative approaches to modelling carer QALYs that consider the following three key points: 1. Extension to patient life granted by risdiplam is of substantial value to carers. 2. The benefit of risdiplam to carers associated with delaying bereavement. 3. The QoL gained by carers through improved functional ability of the risdiplam-treated patients under their care. These three points are discussed further below: 1. It is the company's firm belief that the extension to life granted to patients by risdiplam is of substantial value to carers, who are very commonly family members of the patient. The company strongly do not believe that carers would trade-off caring for a patient for a longer period of time in favour of the patient experiencing an early death. As such, to reflect this, in the company's revised modelling approach, the ERG's original approach to modelling career disutility is adopted, however, carer QALY losses in the risdiplam arm associated specifically with extension to life over BSC have been disregarded from the analysis. This has been achieved through removing any further carer QALY losses associated with both risdiplam and BSC following the point of mean survival for the BSC arm in the model. The approach is in line with feedback from the Committee that they would like to see the impact of the analysis if carer disutility is no longer counted after death of the BSC patient. 2. As noted in the ACD, patient experts confirmed that bereavement would have a significant and sustained effect on carer QoL.[3] Therefore, a carer disutility for bereavement (-0.04 based on Song et al. [2010][13]) has been included, in line with the ERG's proposed approach at the first Appraisal Committee meeting. This QoL decrement has been applied from the point of mean survival in each treatment arm for the remaining time horizon, reflecting the extensive duration carers are likely to feel the loss of the patient. 3. As demonstrated by the clinical data, risdiplam results in functional gains in patients, which in turn enable patients to express a greater level of independence and reduces their dependence on the carer. Roche would therefore like to highlight to the Committee that the patients' functional gains resulting from risdiplam treatment also positively affect carers' QoL. This aspect was captured in both the company's and ERG's original approach, and Roche has continued to capture this aspect in the updated models. Roche's revised modelling approach summarising points 1–3 are represented on the graphs presented in Figure 1.	FAD.

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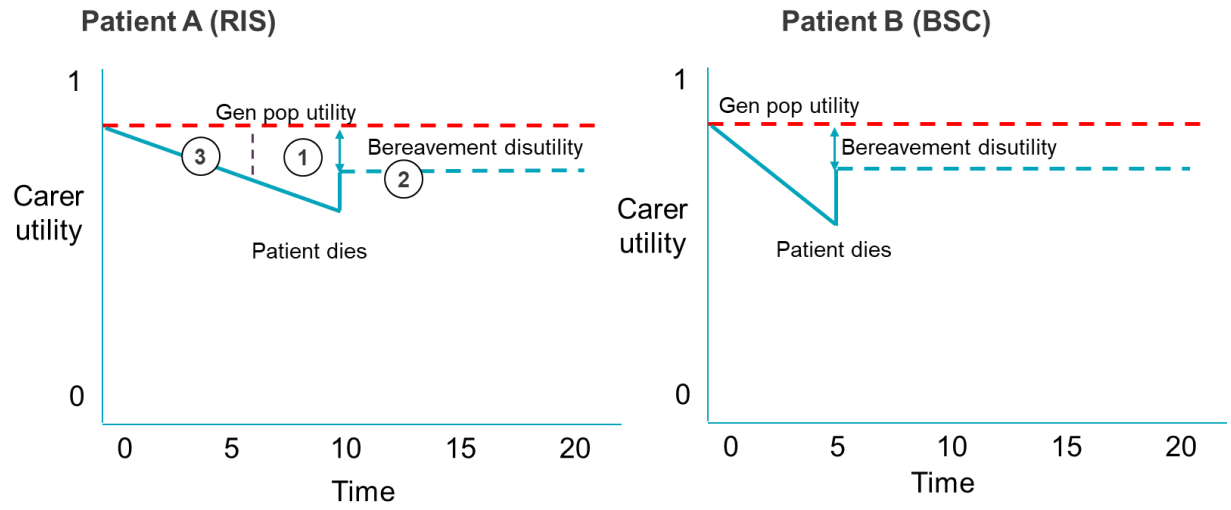
			Figure 1. Illustration of company's revised approach to modelling carer disutility  **Key: 1.** Area indicated by '1' represents carer QALY losses associated with extension to life with risdiplam compared to BSC (disregarded from revised modelling approach); **2.** The disutility associated with bereavement is delayed through the extended life with risdiplam treatment compared to BSC (included in revised modelled approach); **3.** Reduced carer QALY losses with risdiplam treatment compared to BSC resulting from patients' functional gains (included in the original and revised modelling approach). **Footnote:** Numbers on the graphs are arbitrary and for illustration only. The following assumptions are made: carer utility declines with time as patients' functional status worsens. Patients' functional status declines at a faster rate with BSC compared to risdiplam. Patients treated with BSC die at an earlier timepoint compared to risdiplam. **Abbreviations:** BSC: best supportive care; Gen pop: general population; QALY: quality-adjusted life years; RIS: risdiplam Despite the modelling approach for carer disutility described above resulting in reduced carer QALY losses per risdiplam patient compared to a BSC patient, carer QALYs in the risdiplam arm still accrue a greater negative total compared to the BSC arm in the base case. This is due to the fact that within the model cohort, a greater proportion of risdiplam patients are alive at any given point in the time horizon compared to BSC (until all patients have died). As such, a greater negative carer QALY loss is accumulated in total in the risdiplam arm compared to the BSC arm. Given this result remains contrary to the Committee's preference that including carer QoL should not result in the accumulation of fewer QALYs, an alternative analysis has also been presented for the Committee's consideration, in which a	

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			'cap' has been applied to the total carer QALYs in the risdiplam arm for each health state, such that QALYs cannot exceed a more negative value than the BSC arm. This is more aligned with committee conclusions, however it is still a conservative approach as it assumes the caregiver quality of life is the same across the treatment arms. The ICER of this analysis is £[redacted] (please see appendix for further details). As both of the above analyses are conservative, Roche felt it was important to highlight that when applying the additive approach to modelling caregiver QALYs, the ICER is £[redacted] (please see appendix for further details). Although Roche recognises the limitations of this approach, it is still a method encouraged by the NICE DSU on modelling caregiver QALYs, and highlights the impact the modelling has on the ICER. It is therefore plausible to consider that the true ICER lies within this range. Due to the approach to modelling carer QALYs being less problematic in the type 2/3 model (and therefore not associated with the equivalent ethical issues as type 1), the ERG's original approach to modelling carer disutility has been applied in the base case, and the revised carer disutility modelling approach is applied in a scenario analysis, resulting in an ICER of £[redacted]. In addition, as per the ERG's preference for alignment with TA588, three carers have been assumed for the 'not sitting' state in the type 2/3 model base case. Overall, the carer QoL gains with this new approach are supported by clinicians and a carer expert confirming that QoL would not be lower if a patient was on risdiplam compared to BSC.[10] As indicated by the SUNFISH data outlined above, carer-reported independence as measured by SMAIS increased after 12 months with risdiplam treatment, and this increase was built upon subsequently as demonstrated by the 24-month data.[1] This increase in independence with risdiplam treatment translates to improved QoL for both patients and carers. Additionally, risdiplam patients overall are assumed to be in better health states than BSC patients whilst they are alive, and this functional gain combined with carer QoL loss from bereavement being delayed results in overall improved carer QALYs. Roche acknowledges that the approach may still not represent complete likeness to the real-world scenario, and would like to ask the Committee to consider flexibility in decision making, given the challenges to accurately model the effect of risdiplam treatment on carer QoL.	
8	Company	Roche UK	**Bulbar function, respiratory and scoliosis disutilities and costs** During the first Appraisal Committee Meeting, Roche noted that some benefits of risdiplam treatment, such as improvements in respiratory and bulbar function (including swallowing, vocalising and the ability to communicate), were not adequately captured in the models submitted at technical engagement.[3] The Committee was in agreement with Roche that there are likely to be benefits of risdiplam treatment that are not captured in the original models.[3] As such, Roche has updated the models to incorporate additional important aspects of SMA as a disease, in addition to motor milestone achievement, such as scoliosis, requirement for respiratory support and bulbar function. A recent study that subdivided patients into type 1a–c, 2a–b and 3a–b reported that the probability of scoliosis surgery across a patient's lifetime was ~80% in patients with type 1c and 2 SMA, indicating that scoliosis is a common problem affecting the QoL of SMA patients.[14] The requirement for respiratory	The company considered these analyses. See section 3.16 of the FAD.

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			support in SMA is broadly accepted, with particularly type 1 SMA patients frequently developing respiratory failure prior to 2 years of life.[15] Additionally, a recent study indicated that patients with type 2a SMA experience a rapid decline in respiratory function, needing respiratory support (>16 hours/day) at a mean age of 20 years.[16] Published evidence also confirms that SMA patients frequently encounter bulbar problems, including problems with chewing, swallowing and choking.[17,18] One patient expert that Roche consulted with shared their experience that treatment with risdiplam improved their swallowing function and that this allowed them to eat a wider variety of food with less concern about choking, which impacted both her physical and mental wellbeing.[10] Therefore, disutilities associated with scoliosis, decline in respiratory function and bulbar problems have been applied to the updated type 2/3 and type 1 models, and corresponding costs have additionally been included. Clinical expert opinion confirmed that especially type 1 and weaker type 2 patients are likely to lose bulbar function.[10] Specifically, a clinical expert noted that non-ambulant patients are more likely to experience scoliosis, poor respiratory function and bulbar problems, and that these problems are often exacerbated in non-sitters.[10] Therefore, a disutility for each impairment has been introduced in the "not sitting" and "sitting with support" health states in the type 2/3 model base case, and "permanent ventilation" and "not sitting" health states in the type 1 model base case. The following disutilities have been applied: -0.17 for bulbar function (derived from Lloyd et al. [2019][19]), -0.085 for scoliosis (derived from Part 2 of the SUNFISH clinical trial) and -0.07 for respiratory function (derived from Part 2 of the SUNFISH clinical trial). Costs associated with these impairments were sourced from relevant NHS reference costs and applied to the relevant health states; frequencies-per-cycle for the application of each of the impairment-associated costs were informed by a Burden of Illness study conducted by Roche in the UK. Additionally, the proportion of patients experiencing these issues could be expected to be lower in the risdiplam arm in comparison to the BSC arm. As such, an assumption has been made that 100% of BSC patients in these states would experience these impairments, with this value changing to 50% in the risdiplam arm. This is informed by feedback from clinical experts that bulbar function, respiratory ability and scoliosis are all highly interlinked, and they would expect patients to benefit in all three areas upon treatment with risdiplam, across all types of SMA.[10] In addition, the strength of the data seen in these patients to date demonstrates this can be considered an appropriate assumption.	
9	Company	Roche UK	The ERG additionally noted that the plateau time point in the models (month 26 for type 2/3 SMA and month 66 for type 1 SMA) had previously been applied one month too early. Roche would like to confirm that this has been rectified in the updated model.	Comment noted.
10		Clinical expert	I have some concerns about best supportive care being used as the comparator for Risdiplam treatment The vast majority of children and young people presenting with Spinal Muscular Atrophy (SMA) are now receiving treatment with disease modifying drugs Nusinersen has been available for those with SMA type 1 and 2, and for those with type 3 SMA who remain ambulant since the opening of the Managed Access Agreement (MAA) in July 2019 and prior to that via the Company's Extended Access programme for those with SMA type 1 Those with SMA type 3a who had lost ambulation were originally excluded from treatment under the	Nusinersen is only available on the NHS as part of a managed access agreement. It is not routinely commissioned and

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			MAA, but following NICE review of the evidence in April 2021, these patients can now access treatment Effectively only those with complex spinal anatomy or in whom repeated Lumbar puncture (LP) is not safe or feasible are now precluded from treatment. Initiating Nusinersen treatment in the adult population has been a more protracted process and there are adults managed by NM services that have not been able to deliver the treatment for practical reasons Since the opening of the EAMS in 2020, many of these individuals are now receiving Risdiplam Onasemnogene treatment for infants < 13m with type 1 SMA is now being delivered in the 4 infusion sites selected by NHSE. Older infants and children with SMA type 1 < 21kg in weight are also able to access treatment via the NHSE agreement with Novartis. Therefore in practice the majority of children and young people are receiving disease modifying drugs and not best supportive care. In my service, I manage 41 children < 19 yrs with SMA. 27 are receiving Nusinersen, 10 are receiving Risdiplam via the EAMS, and 2 are presymptomatic, with 1 awaiting treatment with onasemnogene next week and only 1/41 children (an ambulant SMA type 3 patient) receiving best supportive care. This is likely to be the case for the majority of children's SMA centres across the UK Thus clinical experience from a large centre confirms that there is an unmet need for an SMN2 modifying drug that can be delivered orally (25% of our children's cohort) but also that very few children and young people are simply receiving best supportive care	so cannot be considered as a comparator.
11		Clinical expert	I also agree with the committee's view that the company's model overestimates the life expectancy of those whose SMA type 1 is managed with best supportive care, as the figures generated do not reflect clinical experience. I believe it would be more accurate to model the survival in the untreated group on data from natural history studies (Finkel et al) and indeed the control arm of the Endear study	Comment noted.
12		Clinical expert	I agree that there is no peer reviewed data to determine the long term effect of Risdiplam and that it would be appropriate to include some form of 'stopping' criteria for its use, along the lines of the MAA for Nusinersen. It would not be appropriate to continue to prescribe the drug if there was no evidence to support its effectiveness. The committee have agreed with patient and clinical experts that stabilisation of functional abilities is a positive outcome in a progressive condition like SMA. In my experience, it is possible to apply a combination of standardised functional assessments in a systematic and objective way to identify those whose condition has failed to respond to treatment. However, it is important to 'select' the appropriate tools to capture the full range of benefits of treatment. Crude assessment of motor milestones will fail to pick up more subtle benefits in fine motor skills and upper limb function that are of significant value to individuals and their ability to participate in society,	Comment noted. Please see section 3.17 of the FAD.

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			maintain their independence and lead good quality lives. However, given the challenges and complexities of applying such assessments, it may be possible that a combination of 'time' with the most appropriate functional and QofL assessments could be used The clinical benefits seen in the respiratory and bulbar function of a systemically delivered treatment like Risdiplam have not been adequately captured in the models, although the trend in improvements can be seen when comparing the outcomes at 1 year of treatment with Nusinersen (Endear) and Risdiplam (Firefish).The benefits will not only impact individual patients but also their care givers and hospital services. Respiratory impairment results in recurrent infections and hypoventilation and is the most likely cause of unplanned and protracted hospital admissions in SMA, including admission to critical care units. It is the main factor underlying the reduced life expectancy seen in SMA types 1 and 2	
13		Clinical expert	I agree that the Health utility values used to identify the gains in upper limb function underestimate the beneficial effects of treatment. Maintaining the capacity to independently transfer, dress and feed oneself are hugely significant. Preserving or improving fine motor skills can mean the difference between participation in education/workplace activites as well as being able to operate controls for powered chairs/equipment and the environment. Such 'control' is vital to emotional and psychological well being and should equate to a higher HU score The reduced burden for caregivers, outlined powerfully by patient experts should also be captured in the model. The costs benefits of reduced 'face to face' care needs and potential for active participation in the workplace should also be considered	Please see section 3.16 of the FAD.
14		Clinical expert	I have concerns about a model that assumes that premature death of an infant with SMA 1 is somehow beneficial to caregivers and feel this is an unacceptable position. In my experience this is not the case, infants with SMA type 1 have good cognition and even very weak infants enjoy positive interactions with their family and loved ones. Recurrent hospital admissions to support feeding and breathing difficulties have a considerable impact on the child and family's quality of life and the extent and severity of respiratory impairment is the most important factor determining life expectancy. Failing to model the benefits of Risdiplam on bulbar and respiratory function, and simply focusing on gross motor milestones will underestimate the cost benefits of therapy	Please see sections 3.14 and 3.16.
15		Clinical expert	Without Risdplam, a considerable number of SMA patients will be left without access to any disease modifying drugs, particularly those with late onset type 2/3 SMA with complex spinal anatomy and those who cannot tolerate repeated lumbar puncture. Untreated, these patients will decline in their functional abilities, becoming more dependent on carers and clinical services particularly when the inevitable changes in respiratory and bulbar function occur (Trucco et al) By failing to consider the comparative costs of other licensed disease modifying drugs, and their delivery, and by using models that fail to capture the wider functional benefits of treatment, we risk failing to deliver effective therapeutic treatment to a large subgroup of SMA patients increasing the burden of disease to the individual, their carers and health care providers.	Risdiplam has been recommended as part of a managed access agreement.

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16		[Adult SMA REACH, Newcastle University and Newcastle upon Tyne Trust]	We are concerned that people with complex spines likes scoliosis or spinal surgery, who may technically be eligible to Nusinersen, will either not receive any treatment because more challenging or need to undergo a more invasive and higher risk repeat procedures. This group of patients is likely to also have respiratory insufficiency which will contribute to the high risk. We are concerned that this group is discriminated because of their severe disability. An oral treatment is for this group a more suitable option	Risdiplam has been recommended as part of a managed access agreement.
17		[Adult SMA REACH, Newcastle University and Newcastle upon Tyne Trust]	In our clinical practice we observe that fatigue and endurance are also relevant in SMA. these have not been assessed in the clinical trials and data submitted but may and will be available in real world setting but contribute to patients independence	Comment noted.
18		[Adult SMA REACH, Newcastle University and Newcastle upon Tyne Trust]	An oral treatment may be more suitable for patients who have an active life (higher education, job, family, social) and choose to avoid hospital appointments	Comment noted.
19		[Adult SMA REACH, Newcastle University and Newcastle upon Tyne Trust]	Data on effectiveness of risdiplam post exposure to Nusinersen should be available in real world data setting because some patients have been switched when the administration of Nusinersen was no longer suitable	Comment noted.
20		[Adult SMA REACH,	We have concerns that over the past year patients who were eligible to Nusinersen, were not started on treatment because of the COVID-19 pandemic having affected many wards and departments resulting	Risdiplam has been

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		Newcastle University and Newcastle upon Tyne Trust]	in only few adult SMA centre starting adults on Nusinersen. The likelihood is that this will continue for some time. An oral treatment would result in patients accessing treatment earlier which would avoid further decline	recommended as part of a managed access agreement.
21		[Adult SMA REACH, Newcastle University and Newcastle upon Tyne Trust]	From our clinical experience and data presented, in adult SMA a meaningful change is to be expected over the 24 months of treatment with some benefit which may be observed even sooner but may not necessarily be statistically significant	Comment noted.
22		Treat SMA	Has all of the relevant evidence been taken into account? Most of the relevant evidence has been accepted. However, we feel that not all has been reviewed to suitable degree or interpreted to it's full extend. For example, TreatSMA submitted survey results clearly showing that in an untreated population the decline is inevitable (10 years timeframe) and that stabilisation (at least) is achieved in the treated population. However the treatment assessed on how much gain is observed in very short (2-3 years) time span. It is expected that over 10 years period the difference would be more significant, but as this new drug, it cannot be observed just yet.	Comment noted. This data was available in the committee papers/
23		Treat SMA	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Whilst we feel a good effort has been put into summaries of clinical and cost effectiveness, the true impact of the treatment on patients health and real life is underestimated. Clinical record of moving fingers does not score points on scales and therefore does not add points to the economic model. On the other hand it allows person to use power wheelchair to move around. Increase in vocal strength has zero points on scales on no impact on the model, but it can get voice activated IT to work better or allows child to participate in school activities more. These little nuances are not taken into account, but they have massive impacts on the life of individual and therefore should affect the cost effectiveness of the treatment. Furthermore, we completely disagree with the model used for the loss of life and impact it has on caregivers and parents. The impact is dramatic and negative and very long lasting. Majority of the	Comments noted. Please see sections 3.14 to 3.16 of the FAD.

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			families we know have not gotten over this tragedy and continue to suffer mentally and expressing it physically - substance abuse, self harm, eating/drinking disorders, suicide(s) to name few. All of which has long term implications on NHS resources.	
24		Treat SMA	Are the recommendations sound and a suitable basis for guidance to the NHS? No. We believe this is not the case. We feel that the really sticky point is the costs of the treatment. Therefore, we feel that pharmaceutical company and NHSE must find a financial agreement to resolve the difficulties and thus paving the way for suitable recommendations from NICE.	Risdiplam has been recommended as part of a managed access agreement.
25		Treat SMA	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? No.	Comment noted.
26		Treat SMA	TreatSMA believes that a negative outcome of this appraisal is not acceptable and leaves significant prevalent population of people with SMA unable to access much needed treatment. We feel that evidence and models used in the assessment do not illustrate the picture to its fullest. The benefits gained by patients are undervalued in commercial model and viewed from basic heath economics without translation of how this gains/stabilisation impacts people in real life. In short we feel that there is more work that needs to go into this and most importantly the costs of the treatment should also be looked at by company.	Risdiplam has been recommended as part of a managed access agreement.
27		SMA UK and MDUK	We are disappointed by NICE's initial 'no' to recommending risdiplam for NHS funding.	Risdiplam has been recommended as part of a managed access agreement.
28		SMA UK and MDUK	Has all of the relevant evidence been taken into account? NICE's summary indicates that the committee heard, and has taken into account, the evidence put forward by clinical and patient experts. We welcome this. Please see further related responses in comments 3 - 6.	Comment noted.
29		SMA UK and MDUK	The classification system discussion 'the committee acknowledged the limitations of the current SMA classification system but concluded that it had been used in the marketing authorisation and clinical evidence for risdiplam'. (3.2) We hope that, for all the reasons stated in our original submission and presented at the 'NICE Review of access for those with SMA Type 3 to nusinersen', this conclusion confirms that if risdiplam is finally recommended, there will not be any barrier to access based on the clinical classification SMA Type 1, 2 or 3 of a child, young person or adult's SMA.	Risdiplam has been recommended as part of a managed access agreement across types 1-3.
30		SMA UK and	The impact of SMA	Comment noted.

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		MDUK	'The committee concluded that SMA has a substantial effect on the quality of life of patients, caregivers and their families'. (3.3) We are pleased that this patient group evidence has been heard and is considered. We note however, that there remains a debate over caregiver QALYs – please see 13. below.	
31		SMA UK and MDUK	**Risdiplam is an Innovative treatment that will meet an unmet need** Patient groups, '*commented that an oral treatment option would be welcome and would also address several issues related to the delivery of nusinersen including the use of sedation, radiographic imaging and anxiety associated with lumbar puncture*.' (3.4) *'supportive treatments do not affect disease progression, so people with SMA will ultimately become dependent on their families and carers'*. (3.4) '*treatment options used routinely in the NHS in England are currently limited and there is an unmet need for people with SMA1' (3.4)* As described in all submissions from patient and clinical experts, a treatment that may be administered at home is a hugely important option. It avoids the costs and logistical challenges to adults and families with children of regular, lifelong travel for treatment. It also eliminates the need for a particularly invasive procedure that is not possible for many with SMA.	Risdiplam has been recommended as part of a managed access agreement.
32		SMA UK and MDUK	The future possibility of switching between treatments 'The NHS England commissioning expert described the potential treatment pathway if risdiplam were to be recommended as a treatment option alongside nusinersen and onasemnogene abeparvovec. They explained that repeated treatment switching would only be expected in exceptional circumstances, related to issues such as fertility or side effects.' (3.4) We were pleased to hear this open discussion and that the need for this possibility has been acknowledged. If risdiplam is recommended, we would ask however that the following is taken into account: 'The committee recalled that some people who have had nusinersen may have preferred not to have it, but it was the only option available' (3.4) The committee also noted that 'the company stated that there is no plausible biological rationale to expect the treatment effect to differ based on prior treatment because both nusinersen and risdiplam have a similar mechanism of action (they are both SMN2 RNA splicing modifiers).' (3.6)	Comment noted. After consultation the company presented interim results from JEWELFISH. This included some patients that had nusinersen previously. The FAD has been updated to note that "Risdiplam may be effective for patients who have had nusinersen".

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			If risdiplam is recommended, we would want all those currently receiving nusinersen to have discussions with their clinical team and the opportunity of switching treatment and, unless there is a clinical safety issue, the possibility of a switch. We hope that the company's assurance as above and the trust we have in our clinical colleagues will mean that the committee's comment that it 'concluded that it had not seen any evidence for people who have had nusinersen and agreed to take this into account when making its recommendations' (3.6) would not prevent such a recommendation. We hope that the company's comment above that was noted by the committee, will provide sufficient evidence to support switching in any of the circumstances described in this section.	
33		SMA UK and MDUK	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Clinical effectiveness Clinical trials The summaries of the clinical trials provide the base case for NICE. We note the SUNFISH age criteria of 2 – 25 years and that the study excluded patients clinically classified as SMA type 3 SMA who were able to walk. We would be concerned if the lack of evidence for this group were to lead the committee to conclude that this group should be excluded for access to treatment. We reiterate this comment from our survey respondent included in our original submission that summarises the progressive nature of this condition: "The diagnosis needs to be as dynamic as the condition…The etymology of the disease dictates that wherever people start on the continuum of SMA they are on an ever-decreasing scale. As such if you start as a type 3 or type 2 eventually those people have the same end point." We note that FIREFISH - 41 patients aged 1 month to 7 months with type 1 SMA and two SMN2 copies, excluded patients who had previous treatment and those having chronic ventilation. We are keen for clinicians to comment to NICE as to whether these exclusions would be appropriate in the real world setting and for NICE to hear and respond to this. We are also keen for assurance that these criteria would not be used for others seeking this treatment. We are aware there was no restriction on ventilation support for the risdiplam EAMS and know of two adults, unable to access nusinersen, who would not be able to access treatment if this was a criterion for exclusion. They have both been relieved to be accepted on the EAMS and finally have the opportunity for treatment. Both are supported by 24 hr ventilatory support, live full work and leisure lives and are seeking stabilisation of their condition.	The conditions of the managed access agreement do not exclude people with type 3 SMA who are able to walk. The starting criterion of no permanent ventilation was discussed during the development of the managed access agreement, with input from patients and clinicians. It was agreed to include this criterion but to

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			We note that clinical trials have age restrictions to protect the integrity of their data. We are pleased that NICE noted that children are diagnosed with SMA Type 1 later than 7 months and are keen that there is no diagnosis age limit for access for children with SMA Type 1. We note that 'The committee agreed that the clinical evidence showed improved motor function with risdiplam but noted that overall survival data were only available for type 1 SMA' (3.8) We would not expect to see survival data for SMA Type 2 and 3 given that the natural history life expectancy for the participants would have exceeded the length of the clinical trials. In terms of long-term outcomes, it is ethically challenging to expect a long term 'placebo-controlled period' (3.9) in a rare condition where patients are declining progressively when a treatment has been shown to have efficacy.	add that patients who do not meet this criterion but otherwise meet the eligibility criteria should be discussed with the NHS England Clinical Panel. There is no diagnosis age limit for people with type1 SMA.
34		SMA UK and MDUK	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Clinical effectiveness Real world evidence We are pleased to see that the committee noted, 'The patient experts described their experiences of using risdiplam and noted improvements in motor function, lung capacity, energy levels and stamina. They explained that even very small improvements in fine motor skills and upper limb function were very important because they allow patients to maintain independence. They emphasised that although the studies showed improvements in motor function, they would also highly value a treatment that keeps the disease stable and stops it getting worse'. (3.8) We cannot emphasise enough the importance of the outcome of achieving stabilisation as highlighted in our submission and evidenced by the 2019 SMA Europe's Community survey In 2019, when 96.7% of 1,327 validated responses stated they would "consider it to be progress if there was a drug to stabilize their current clinical state." We note also, 'The clinical experts explained that there was considerable uncertainty about the long-term benefits of risdiplam but in their clinical experience the results were promising' (3.9). We also noted a final comment at the committee hearing from one of the clinical experts who stated that their early experience of caring for people enrolled in the risdiplam EAMS was that she was noting an impact on swallowing and respiratory function. This was also raised by the adult patient expert in their evidence following a relatively short time (some months) taking risdiplam.	Comment noted.
35		SMA UK and MDUK	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Cost effectiveness We were encouraged at the committee meeting to hear that the company and ERG, were both willing to	Comment noted.

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			discuss the challenges of the economic modelling and report back to NICE. Please see further comments in 10 – 14.	
36		SMA UK and MDUK	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Cost effectiveness Utility values – fine motor skills We draw attention to the following comment which is one we hear echoed in the SMA community many times 'The patient experts described the importance of maintaining upper limb function because it allows independence. They explained that some benefits were not captured in the available motor function scales because even small improvements were highly valued by patients and made a large difference to health-related quality of life'. (3.12) We consider there is a need to adjust the modelling to reflect this in a way that incorporates a 'utility gain to reflect risdiplam's potential benefits in fine motor skills' (3.12) and that it is, as the committee suggests one that reflects their observation that 'The company's utility gain for fine motor skills is acceptable but may be too low'. (3.16)	The committee considered updated analyses from the company. Please see section 3.16 of the FAD.
37		SMA UK and MDUK	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Cost effectiveness Utility values – other benefits We agree with this comment: 'The company suggested that the models do not adequately reflect all potential benefits of risdiplam because the benefits of improvements in respiratory and bulbar function (such as swallowing, vocalising and the ability to communicate) may not have been adequately captured in the models'. (3.17) We note that 'The committee concluded that there could be some benefits that are not captured in the models' (3.17). We hope to see adjustments to the modelling that reflect this.	The committee considered updated analyses from the company. Please see section 3.16 of the FAD.
38		SMA UK and MDUK	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** **Cost effectiveness** **Caregiver QALYs** We are concerned that this modelling resulted in, '*The counterintuitive results in the type 1 model meant that a life-extending treatment was considered less cost effective when including caregiver utilities (see section 3.13)*' (3.22) and hope that this will be addressed. We are not health economists but suggest that modelling needs to reflect the differences that SMA UK's experience suggests occur – see our summary below. (Please note this was a table 2 x 2 which is easier to follow but this template does not allow this) **Caregiver Type 1 <u>– infant with no treatment - best supportive care</u>**	The committee considered updated analyses from the company. Please see section 3.15 of the FAD.

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			➢ **During infant's lifetime – compared to treated infant** **Impact is more intense but for shorter period** • Night and day care 24/7 – very intense and increasing – ongoing chronic care and acute issue • Frequent hospital admissions – disruption to family life / work / siblings • High stress and depression – no hope • Lack of sleep and fatigue • Lack of social contact • Guilt – genetic inheritance • Intense use of equipment at home • Marital stress • Impact on other siblings • Loss of work – invariably one carer at least - financial impact • High impact on extended family – need for their support and of friends and family ➢ **After death– compared to treated infant** **Impact may be similar** • Grief/ Depression / ongoing mental health impact – on carers and siblings • Not infrequent marital / family breakdown • Return to work /social life challenges We note also that as clinical evidence suggests the earlier the treatment, the more positive the outcome, the assumption that treatment leads to care equivalent to Type 2 may be incorrect and caregiver impact may potentially be reduced further than outlined below. **Caregiver Type 1 – <u>infant with treatment</u>** **Based on assumptions that treatment is given early, infant responds well and moves to at least Type 2 / 3 care needs** ➢ **During infant's lifetime - compared to non-treated (best supportive care)** **Impact drops for some aspects but increases for others and new pressures emerge over time** **Decreases:** • Night and day care hours– chronic needs decrease, acute episodes become less frequent • Hospital admissions • Hope decreases stress and depression • Lack of sleep and fatigue - improves • Lack of social contact – may improve	

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			• Guilt – genetic inheritance –may be less as able to address this better via treatment **Increases** • Equipment and adaptation needs **Not known:** • Marital stress may continue due to sustaining care • Impact on other siblings may continue due to sustaining care • Loss of work – may continue until FT education is possible - financial impact **After death** **Impact may be similar** • As family has been able to do all possible for their child during their lifetime this may help with feelings of guilt and depression **but** Other impacts of grief and loss remain for all affected	
39		SMA UK and MDUK	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** **Cost effectiveness** **Stopping rules** We note this comment, '*Clinical advice to the company suggested that a time-based rule may be easy to implement in the NHS in England and may be preferred to the current criteria set out in TA588 because it would avoid pressure for continuous motor milestone improvement. The clinical and patient experts agreed that the current stopping rules in TA588 were problematic and put undue strain on patients and their caregivers'*. (3.11) *'the committee concluded that the company's stopping rules may not be appropriate, and it would like to see stopping rules based on clinical criteria that have been agreed with clinical and patient experts'* (3.11) We suggest that these comments were made prior to work following the NICE nusinersen access for those who have SMA Type 3 decision, that led to a revision of these stopping rules. These new measures have been agreed by clinicians and patient groups. They now reflect the desired outcome of stabilisation and greater flexibility in terms of the use of scales and measurements that will reflect this and that recognise the importance of stabilisation of fine motor skills. There is a lay summary here: https://smauk.org.uk/blog/treatments-research/how-scales-and-measurements-will-work-now-for-englands-maa-for-nusinersen We acknowledge the limitations of scales that are insufficiently sensitive to capture subtle changes and that currently the all-important Patient Reported Outcome Measures (PROMS are not collected. We suggest that this information is important for any future decisions and to assist with ascertaining which	Comment noted. The section of the FAD relating to stopping has been updated.

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			drugs work better for which groups. We are aware that this does present extra work and time for clinicians, in particular physiotherapists, and can be onerous for families / adults but imagine that they would all welcome the opportunity to add to the pool of knowledge about treatment efficacy. If measurements and stopping rules can operate without NICE / NHSE's involvement but as part of clinical research funded via other routes, we would be in favour of this possibility.	
40		SMA UK and MDUK	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** **Cost effectiveness** **Price** We hope that every effort is being made by the company and NHSE's commercial arm to reach an agreed price that will allow this treatment to be recommended.	Risdiplam has been recommended as part of a managed access agreement.
41		SMA UK and MDUK	**Are the recommendations sound and a suitable basis for guidance to the NHS?** Until such time as the economic modelling issues and costs have been addressed, we don't consider the 'no' to NHS funding recommendation to be a sound and a suitable basis for guidance to the NHS. The consultation paper notes *'Risdiplam has features that are commonly seen in treatments assessed by the highly specialised technologies programme, but it was considered as a single technology appraisal.*' (3.21) The committee assures us that '*The decision making takes into account the rarity and severity of the disease'* (3.21) We remain concerned by the constraints of the STA system. We point out that nusinersen treatment was recommended following considerable work on the economic modelling and costs and that this was within the STA framework. We suggest that the clinical and real-world evidence of effectiveness for risdiplam heard by the committee is as robust as possible for any new treatment for a rare condition and note its innovative nature. We remind everyone involved in this appraisal, that for people who live with this progressive condition, every day counts and that their lives could be changed significantly and positively by this treatment. We would therefore expect work on the economic modelling and price to conclude swiftly and positively. We would expect NICE to enable any flexibility the STA process allowed for nusinersen to be enacted for risdiplam, resulting in a positive recommendation.	Risdiplam has been recommended as part of a managed access agreement.
42	Web comment		• Has all of the relevant evidence been taken into account? I have expressed many of our thoughts in the close questions. However, the other significant situation as parents is that we have always been open with our son about his SMA2 and why we do things but recognise (as with so many children with SMA) that he is a bright boy, who as he gets older, should be involved in the decision making process (just as he is about who his carers are and how they might help him etc). It did not sit comfortably with us to force him to take nusinersen just because we fulfilled the criteria, especially when we weren't sure how significant an impact it would make. The relationship we	Thank you for your comments. Risdiplam has been recommended as part of a managed access agreement.

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			have with our son is paramount as we, as a family, will continue to have to face many things together and we negotiate life living with a disability. For any treatment to be a success, we know that we need him to be 'on board' as he is well aware that this is his body which he can make choices over. As I said, children with SMA often have a heightened emotional and social development, and are very 'switched on'. He was not 'on board' with nusinersen, and whilst we have kept the conversation open, it has been hard to promote such an invasive, medicalised and potentially risky procedure despite all its potential benefits. Knowing that risdiplam is a future possibility gives him hope. Our sadness is that we were not allowed to be part of the Early Access Programme even with his strong aversion to needles, and the spinal procedure, because technically and clinically he met the criteria for nusinersen. It has put us in an impossible position where we could risk our relationship with him if we forced this decision which could then have an impact on his mental and physical well being, his education, his right to an opinion which he should be able to express and should be listened to and heard. This may not be measurable evidence but it is a real experience. So we are now in the situation, where our ideal approach of risdiplam which suits our son, and our family hangs in the balance whilst we have to re-visit again the anxiety of looking at nusinersen which may end up having a more negative impact on our lifestyle as more time in school will be lost. Our son is also being made to be even more aware of his 'disability' as an issue when our approach has always to be to get on with things so that he can be like everyone else. He doesn't like the attention of being 'different' not because of his powerchair but because he often has to miss what his friends are doing at school because of appointments! It is hard enough as it is to live in a mainstream world, but our son is a happy, positive balanced boy and we want to maintain that. He dreams big. He lives with a severe disability but doesn't see that should mean he is treated differently. He is prepared to go out there and live and does not want his personality to be defined as his disability. A medication like risdiplam would enable him to keep that attitude whilst doing something proactive to help his condition. He just wants to do the fun things in life. Having risdiplam would also release the neurology teams to focus on those who do need very specific treatments, whilst allowing the rest of us to 'get on with it' with the best possible outcomes. To me that is cost effective. The recent advances for the treatment of SMA are incredible and truly life changing. Those who have SMA are incredible people with tremendous and equal value to everyone else. Having rispdipalm available, will enable those with SMA to live an even more full life and give back to society 100 fold. The approval of NICE would recognise this value. • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? In my opinion, no, as there is more to measuring the worth of something than money alone. This is such an incredible breakthrough that it is worth supporting. • Are the recommendations sound and a suitable basis for guidance to the NHS?	

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			I am re-emphasising these points as many I do believe would have positive impact on the NHS and the individuals involved. The oral treatment of Risdiplam would be of huge significance for a family like ours. We have always just got on with making our life as good as it could possibly be for our son. When nusinersen arrived, it took us by surprise a bit as it suddenly seemed to medicalise our son's condition in a way we hadn't expected, as after we had been for the assessment, we were talking about a very invasive process of lumbar punctures, general anaesthetic and an uncertainty as to what degree this may help. Once our son realised it wouldn't enable him to walk, he completely rejected the whole procedure. He said if he could take something, that would be better as yes he would like to be stronger, but on balance he said he was 'happy in his skin' and didn't want all the needles. We were then faced with a difficult situation as parents as we didn't feel comfortable with 'forcing' an eight year old to go through a very invasive procedure. We felt he would have to be on board, and whilst we have revisited the options, his response was always the same. At this time we began to find out about Risdiplam which seems to offer a family like ours so much more. It could be given at home which would maintain 'normality' of life; it avoided the anxiety of the child and all of the family ahead of each injection whilst seeming to give the same benefits; it appeared to be working well in patients in other countries; it allowed the children to maintain a quality of life that avoided even more hospital visits and professionals in their lives; allowed education to continue undisrupted (an underestimated but highly important benefit); avoided long journeys to the hospital (we are 1.5 hours from the hospital); avoided time being taken off work and additional childcare being sought for other family members; seemed to be a cost effective alternative to injections which are also dependent on a team being constantly in place; removed the anxiety of travel during the ongoing covid pandemic. There are just so many benefits. In addition, having risdiplam would give the patients a choice as to what the best route for them was. To have that choice is of immense value. • Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? The patient voice and a right to choice needs to be heard more. Those making the decisions should listen to the impact on those who give care and live with the every day reality of caring for someone with SMA. • Section 1.1 This is a drug that can be taken at home without impacting on daily life to the extent of nusinersen does (with visits to hospital, blood tests, clinicians, consultants, travelling, anxiety, unpredictability - local	

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			anaesthetic vs General anaesthetic, impact of scoliosis, time lost in education). • Section 1.2 It is unfair that those who may be clinically viable for nusinersen have not been able to make a decision to be on the early access programme for risdiplam if they have a severe aversion to having a spinal injection. It is very short sighted to not have taken into account the mental anxiety and stress that this may cause both to the children and parents. • Section 2.1 All people with SMA should have the opportunity to explore the possibilities with Risdiplam, as it it not a condition that fits neatly into boxes; SMA manifests itself differently in every person who has it despite the similarities in the condition. • Section 2.3 A decision like this should not be based on price. All costs can change, and with a larger audience wanting to receive Risdiplam, then a more effective price should be negotiated. Medicines like this will pave the way for so much more research which will have an impact on many neuromuscular conditions. • Section 3.12 It is hard to explain why even minor improvements might have such an impact on a person. It could even be the difference of being able to press a button to access something independently, or hold a pencil to write for longer than 5 minutes, or hold up an ice cream! These are all every day activities which someone without SMA takes for granted but are of immense value to someone with SMA. It maintains the dignity of a person if they can do some of the small actions. It also means that things like friendships and relationships can happen without constant care and supervision being given. When trying to give an example of the degree to which strength is impacted, I have often used a children's storybook with the buttons to press to make the noise in a book. Our son struggles with that as a 9 year old, with a book designed for a 1 year old. • Section 3.13. If a carer has a more stable condition to work with, then that would enhance the quality of life for patient and care givers. Our challenge is that this is under constant review with all professionals which is time consuming, disruptive and emotionally draining. With more stability, a more pro-active approach to life	

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			can be taken and embedded into every day life. As parents,we know that the situation with our son could change at any moment with the 'wrong' type of cough affecting him and him not having sufficient physical strength to fight it. • Section 3.1 I agree with this clinical description. In addition to this, it should be noted that SMA presents itself very much as a physical condition and those who have it often have a heightened mental capability, with a very strong awareness of the world, a social awareness of how people behave as they work so closely on an intimate level with so many professionals, and a real desire to go out there and live the lives they have been born to live without barriers. It can be a life limiting condition but with our son we do everything possible to mitigate the effects of his disability through attitude and technology/equipment so that he is empowered to contribute to society. The daily physical challenge is immense as are the barriers that have to be overcome but the aim is very much to live the best life possible. • Section 3.2 Yes the boundaries between different types of SMA are blurred, and within each type there is huge range of impact. For example with SMA2 which is what I am most familiar with, some may struggle more with swallowing and eating, others with scoliosis, others with respiratory infections and coughing, reduced upper body strength, weight loss or weight gain, being hyperflexive. SMA 1 is very different to SMA2 or 3 but the need to make a difference is very real. • Section 3.2 When you receive a diagnosis of SMA the immediate impact is of deep, deep shock and sadness, a very real and tangible bereavement as you have to face up to the life that you had dreamed of becoming very different. And then you have to hold your head up and make a decision about the sort of life you wold like to carve out for your child and the approach that you will take. As parents we decided, to live life to the full and create an environment that would allow our son to thrive, to fulfil his potential and to be fully included in society and to enable him to fully contribute to society too. He was to have no barriers to living, and at that point in 2013, there was no medical hope on the horizon, just management strategies. We had to move house which is now fully adapted so that he could have at least one place where everything was accessible and set up for his needs (bathing, hoist, lift, pathways, space for equipment, space for carers) to take some of the everyday pressure away. We have maintained daily physio to give him the best physical chances possible and funded equipment to allow him to access life. When he becomes poorly with chest infections which can develop rapidly, we are on high alert and use early interventions (cough assist, bipap, nebuliser, antibiotics) to minimise the impacts. However, SMA causes	

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			fatigue and he can soon become too tired to even cough and breathing becomes a struggle requiring immediate open access to the hospital. When he gets a cold, the lack of strength becomes frightening. However, we have learnt how to keep the 'medical' impacts to a minimum and as a result he is able to live a 'normal' and fully integrated, good quality life. He is 'happy in his skin'. He attends a mainstream primary school and is doing well. However, the daily routine is hard. He requires 24/7 support for all his physical needs: toileting, dressing, brushing his hair, turning in bed, positioning, cutting food, accessing toys, reaching for things, coughing, lifting up when he falls forward, harnessing when getting into the car....All of this takes additional time and is very physical. It is hard for him to rely on others to the extent he does, so the chance to do anything independently is seized upon: it is important and not to be underestimated. It is painful to watch and realise that your child has lost some of the strength they once had when even lifting a cup of water to their mouth is a big movement, and a tiring one. The financial impact is real, and so is the emotional impact. The whole family is affected, and the whole family is enhanced despite the challenges. Our son asks real questions about what life may be like in the future, he likes to show his 'strength' but as parents we worry about what the future holds for our normal boy who happens to have physical disability. We have to be positive about the future and keep hope. • Section 3.4 The oral treatment of Risdiplam would be of huge significance for a family like ours. We have always just got on with making our life as good as it could possibly be for our son. When nusinersen arrived, it took us by surprise a bit as it suddenly seemed to medicalise our son's condition in a way we hadn't expected, as after we had been for the assessment, we were talking about a very invasive process of lumbar punctures, general anaesthetic and an uncertainty as to what degree this may help. Once our son realised it wouldn't enable him to walk, he completely rejected the whole procedure. He said if he could take something, that would be better as yes he would like to be stronger, but on balance he said he was 'happy in his skin' and didn't want all the needles. We were then faced with a difficult situation as parents as we didn't feel comfortable with 'forcing' an eight year old to go through a very invasive procedure. We felt he would have to be on board, and whilst we have revisited the options, his response was always the same. At this time we began to find out about Risdiplam which seems to offer a family like ours so much more. It could be given at home which would maintain 'normality' of life; it avoided the anxiety of the child and all of the family ahead of each injection whilst seeming to give the same benefits; it appeared to be working well in patients in other countries; it allowed the children to maintain a quality of life that avoided even more hospital visits and professionals in their lives; allowed education to continue undisrupted (an underestimated but highly important benefit); avoided long journeys to the hospital (we are 1.5 hours from the hospital); avoided time being taken off work and additional childcare being sought for other family members; seemed to be a cost effective alternative to injections which are also dependent on a team being constantly in place; removed the anxiety of travel during the ongoing covid pandemic. There are just so many benefits. In addition, having risdiplam would give the patients a	

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			choice as to what the best route for them was. To have that choice is of immense value. • Section 3.8 Absolutely. Any small changes or improvements in function are of immense consequence to someone with SMA and those who care for them. This cannot be underestimated. Our son is hopeful to maintain what he has with the hope of some small improvements. To him, strength is everything, and will enable him to be as independent as possible. It could be the difference to holding a recorder or not; lifting a fork to his own mouth; pulling a door handle open; choosing a book from the shelf. It could help him to cough up mucus more readily instead of it getting stuck on his lungs and causing infection. He could have more energy to do physical activity like hydrotherapy to help him keep fit, burn off some calories and maintain mental well being. With a more stable condition, he can plan things. If you don't know how you'll be in a year's time, that becomes much harder. • Section 3.11 I find these decisions over number of years very difficult to understand. It suddenly feels like a judgement about how many years any one person is entitled to. Every person should have the opportunity to life, and being able to live it to the full. If that is not the case, then those who make those decisions need to look into the eyes of the people who would like this treatment and explain to them why the length of their potential life justifies the outcome of the decision. • Section 3.18 When we received our diagnosis, there was nothing to give any hope, even though we asked those questions. It all seemed very far away as SMA was so rare. Now we are in this position where we could have a choice of treatment, with one being able to be given in our home. That, to me is innovative, and a real achievement; a game changer for us and how we choose to live our life. • Section 3.21 The decision making process should recognise that early intervention is key with SMA and could have significant impacts on families. Those being diagnosed now will have a choice which should allow their children to have more options as they grow up. Those who have waited for so long, should have the opportunity to see how the medications available could have an impact.	
43			• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	Thank you for your comments.

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			I am not sure that you can put a value on the ability to swallow, the ability to breathe unaided.It is multifaceted. If you can swallow,you can eat without need of a feeding tube.You can swallow without risk of aspirating and requiring medication for chest infections etc.You can leave the house and spend time socialising (eating is a social habit) leading to better mental health etc. I am not sure how you assess the cost effectiveness of a medication that can help you keep swallowing.I ask you personally. How much would you pay to be able to swallow food all your life?How much is that worth go you? • Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? I think in an economic and political climate that has been keen to give access to health care to all. (That is a national lockdown to prevent the NHS being overwhelmed and therefore ALL,irrespective of age,disability and underlying medical conditions that require treatment for Covid, be given it),it seems discriminatory to on the other hand deny a treatment to a group of individuals where a benefit in research has been shown.For some, with SMA there are no treatments at all.Risdiplam fills this gap until market alternatives can be found. I am sure that if the threat of SMA was as prevalent in society as Covid 19, a treatment would have been found more quickly and been licenced more quickly.Because a small population is involved, their plight is unheard and their need is unmet.I believe this is discriminatory in itself.To let this small population deteriorate further (as has happened because of delays in licencing nusinersen) really will mean death to some and permanent (and unecessary) long term severe disability to others. The problem with waiting for long term evidence is that by the time the evidence comes in from the rest of the real world studies a lot of time has been lost for those deteriorating with SMA.The function they loose over time can never be regained,therefore there should be a managed access programme to review the medication while this data is collected.	Risdiplam has been recommended as part of a managed access agreement.
44			• Has all of the relevant evidence been taken into account? Serious consideration to young people who are out of scope of Zolgensma, Nusiurnesen but are on the boundaries of loosing significant independence that have their whole life still to live, that having access to Risdiplam is their only current hope. • Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and	Thank you for your comments. Risdiplam has been recommended as part of a managed access agreement.

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			maternity? I would like my specific perspective taken into account and reviewed: After being diagnosed at 18 months old with SMA Type 3, I could walk until 10 and have been completely non-ambulant since the age of 14. I am now 27, I run my own business, compete for GB Paralympic air rifle talent and development squad and have my whole life to live an aspire for. I now find myself in a position due to my spinal fusion at 14 being out of scope for nuisurnersen and potentially never be able to access risdiplam if not approved. To be so young with my whole life to live and still have very basic independence to eat, drink, work and take part in sport, I would love to be able to maintain the limited mobility I have now. The thought of there being two drugs that I cannot access is really starting to effect my mental health, something I have always been in control in. Risdiplam is my only hope to maintain what I have before literally all my independence could be taken away. COVID-19 has caused me to loose a sever amount of muscle mass, whereby I am now struggle to eat my dinner independently, time is critical for me now, I am running out of time before its to late where I am close to losing a lot of my independence. To whom it may concern, I hope this finds you well. My name is [redacted]. I am a Tax Manager working for a 'big four' financial firm. I am a [redacted]. I am an honours graduate from the University of St Andrews. I have been [redacted]. Today, I am not writing to you in any of these capacities. I am writing to you simply as somebody who suffers from Spinal Muscular Atrophy (SMA) Type 2. To my regret, I have never been particularly active in the SMA community. For most of my life, SMA was something I lived with quietly in the background, and although it has always dominated many aspects of my life, I preferred not to think about it too much. However, in late November 2020, the wonderful doctors in the muscle team in Newcastle told me that I was eligible to begin a new treatment program, receiving a daily dose of Risdiplam under the early access to medicine scheme. Suddenly, I was thinking about my condition a lot more, but where there had once been concern and anxiety, there was now a growing optimism. On the 18th of December, a week before Christmas, my family and I received the best festive present of our lives when I took my first dose of the drug. The most truly remarkable aspect of all of this was that this medication was simply 6.6ml of oral liquid.	

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			No injections into the spine, no anaesthetic, no surgical element. In fact, no real impact on everyday life. Incredibly easy to take and, for me at least, no side-effects. For the first 25 and a half years of my life, I was receiving no direct medical treatment for the SMA that was slowly eating away at me, causing my muscles to deteriorate over time. It is difficult to describe the feeling of liberation and hope that I felt on taking the first dose of Risdiplam. It is the memory of that feeling that compelled me to write to you today. Along with many others, I am disappointed with the recent news that NICE is not recommending Risdiplam for treatment of SMA in the UK at this time. I wanted to take this opportunity to share with you some of the details of my journey with SMA so far, along with some of my thoughts following the publication (2nd of June 2021) of the NICE draft guidance on Risdiplam. As with most young boys of my generation, growing up at the very beginning of the 21st-century in North East England, many of my earliest memories take place on playing fields. Although my sporting heroes were often the same, unlike my friends I was never able to recreate a David Beckham free-kick, or attempt a ferocious Alan Shearer penalty. Rather than smash balls for six like Kevin Pietersen, I was always the umpire. I was fortunate enough to grow up with some brilliant people around me. I never felt left out, and my friends and family did all that they could to involve me as much as possible. But there is no escaping the fact that it breaks a young boy's heart to be told he will never kick a ball or hold a cricket bat. This was my first experience of the cruel nature of SMA. Over time, faced with a growing list of things you can't do, it is human nature to start seeking out and focusing on those things you can do. For me, looking back now I guess I decided at an early age that if I wasn't going to be the best at football or cricket, I would make sure I was competing to be the best in the classroom. My early passions for maths and history have stayed with me into adulthood. I studied a maths degree at the University of St Andrews. Moving away to university is an important moment in the life of any young person, and naturally along with that can come a great deal of stress and apprehension. For me this was hugely exacerbated by my condition. Not only was it necessary to contemplate the usual anxieties around moving away from the family home for the first time, but I was also preoccupied with concerns about wheelchair access and the thought of having my care provided entirely by strangers. I fully recognise that I am not unique in these positions that I describe. In fact, I am all too aware that there are many individuals who are in a far worse position than me, including those people who sadly suffer from the more severe form of SMA and who tragically see their lives cut short in so many cases. This underscores the dual nature of the underlying cruelty of SMA; at its most severe, it can rob innocent, infant sufferers of their lives, while those who live on with the less severe forms are instead	

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			forced to watch their bodies weaken over time while their minds continue unaffected. It is not a question of which of these groups have it "better" or "worse". All I can say from my own experience is that it has been helpful to focus on the many special times that I have been lucky enough to enjoy, and the promise of great days to come. There is no better example of the power of Risdiplam than in this simple idea: for the first time in my life, I can now look ahead to the future with a reasonable level of hope that SMA should not take much more from me than it already has. This optimism is not merely blind hope driven only by what I would like to see play out, but instead is based on science and the wonders of modern medicine. With reference to the draft guidance published by NICE, I note that the general consensus appears to be that the committee recognises the clinical benefit of Risdiplam as a treatment for SMA. Indeed, as the guidance states: "the committee agreed that the clinical trials demonstrate that risdiplam meaningfully improves motor function for people with type 1, 2 and 3 SMA." Anecdotally, I can support this conclusion from my own experiences. Around four weeks after taking my first dose of the medication, I noticed substantial improvement in terms of my ability to support my neck while hoisting and to lift my head from the pillow more independently than before. Simultaneously I also noticed improved grip strength in both hands, meaning everyday tasks such as moving a drink to my mouth was suddenly significantly easier. These are the sort of small gains that can be truly transformational in terms of improving the independence of somebody with SMA. My own personal ambition is that hopefully I will also begin to see some additional improvements to my stamina levels as my treatment with Risdiplam progresses. Of course, I fully appreciate that decisions around public health are complicated in their nature. There will be a number of factors to be considered from a range of different areas, so I understand that, along with the clinical benefits that already seem to be fully appreciated by NICE, there are also additional matters for consideration in relation to pricing, health economics, administration and logistics, and the relative merits of other treatments. I am not able to comment on these matters directly. The only contribution I can realistically make at this stage is to reiterate what I have already said: there is a human element to all of this, and although it is difficult to quantify objectively, the sense of hope that Risdiplam has given me truly exists and has enormous value. I hope that this is something you consider as the appeal stage progresses. To conclude, I would like to offer my services in any way that they could be put to use. I would be delighted to engage in any further discussions with any of the relevant parties on this matter - to add the real human voice of a real human being who is currently fortunate enough to be accessing this incredible medicine. Many thanks for taking the time to read this. I look forward to hearing from you.	

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			• Has all of the relevant evidence been taken into account? There is no indication within the ACD that the patient and carer testimonials delivered at the committee meeting have been considered in the decision-making process. These testimonials have been described as “noted” but it is not clear whether they have had any weighting applied to them. Please clarify the extent to which this relevant evidence has been incorporated into the decision-making process. Risdiplam is vital to the SMA population as an alternative to nusinersen. As an oral medication it will be suitable in many cases where a lumbar puncture is simply not an option for the patient. The ACD makes many mentions of there being an unmet clinical need, yet there is little, if any, evidence that the appraisal process really seeks to address that unmet clinical need. My son is 24 years old and has type 3 SMA. We have watched him deteriorate to the stage of being unable to walk and being now wheelchair reliant. Without intervention he will only deteriorate further and lose strength in his upper body and respiratory system. The committee heard a powerful testimony from Andi Thornton who is terrified of losing the one link to independence he now has; the ability to use a computer mouse. I challenge the committee to spend a single day of their lives wheelchair bound with the only movement available to them being the ability to use a computer mouse. This is a future that awaits my son and those with SMA in the absence of their being able to access medication. 24 hours a day, 7 days a week, 52 weeks a year. • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? The ACD is not clear on the price used in the appraisal process. The list price of the drug is the only price stated yet we are aware Roche are prepared to come to a commercial agreement with the NHS. Therefore, if the list price has been used to complete the appraisal, this will produce an artificially adverse cost effectiveness ratio. Please clarify that the price used in the appraisal represents the actual likely cost to the NHS of the medication. From personal experience and from that of friends in the SMA community I can say categorically that the day-to-day stress of living with or caring for an individual with SMA is magnified many times when there is an approved and proven effective treatment that is not being made available to the SMA patient for whatsoever reason. Not only do we have to live with the myriad of “business as usual” challenges, but then there is added stress of the constant battle with the NHS to access medication they should already be providing to us. And, in this case, having to read and attempt to understand long and complex documents so we can feedback on the appraisal process (and that is feedback which we have no real confidence will be taken seriously). There is no evidence in the ACD that any multiplication factor has been applied in the appraisal to the stress levels of the patient and carers to reflect this. Therefore, the stress factor used in the appraisal calculations is understated. Much mention is made in the ACD of “best supportive care” being the best comparator. Clause 3.4 of the ACD refers to “best supportive care” as being intended to “improve quality of life” involving a multi-	

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			disciplinary approach including (amongst others) nutritional support, physiotherapy and occupational therapy. This clause further goes on to state “It is recalled that best supportive care is routinely used in clinical practice in the NHS in England”. If this is what the committee is being led to believe then the committee is being badly advised. By way of example, in our experience (and we are most definitely not alone in our experiences): 1) My son has not had access to an NHS physiotherapy session for over 6 years now. They are simply not available for the adult SMA population. We do daily stretching exercises with him at home; the only professional physiotherapy sessions he has had since turning 18 are those we have paid for privately and those he has been lucky enough to secure through Muscular Dystrophy UK. The NHS neuromuscular centre looking after my son has one part-time physiotherapist to look after over 9,000 patients; 2) My son was diagnosed with SMA in 2004. In the 17 years since then we have not had any form of contact from a dietician or indeed any professional qualified to provide nutritional advice. The subject has never even been mentioned to us; 3) In February 2020 we attempted to secure an occupational therapist’s assessment of Chris’s bedroom and wetroom as we were concerned that the set-up was not safe for him and didn’t know what we could do to make necessary improvements. We were told to expect to hear something within 15 weeks (a long time to wait in any event but particularly when you’ve been clear you’re concerned for an individual’s personal safety). After having to chase we finally got to see an occupational therapist at the end of October 2020 (in excess of an eight month wait). The above details just 3 examples of how my son is far from receiving “best supportive care”. Does the appraisal process take into account that many, if not all, SMA patients are not receiving anything remotely like “best supportive care”? “Best supportive care” is a pipedream and cannot be assumed in the appraisal process. Please confirm that the appraisal process calculations use a “real-life” approach to what is actually available to SMA patients in terms of “supportive care”. • Are the recommendations sound and a suitable basis for guidance to the NHS? The lack of any long-term evidence of Risdiplam’s efficacy should not be used as a determining factor in the decision-making process as there is an unmet clinical need. There is likely to be a lack of long-term evidence with any newly approved drug therefore this is not a credible or fair reason for declining provision of medication where there is an unmet clinical need. The ACD confirms clinical experts having described improvements seen in trials as “promising” and “clinically important”. Further, 3.6 of the ACD refers to nusinersen and states “there is no plausible biological rationale to expect the treatment effect to	

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			differ based on prior treatment because both nusinersen and risdiplam have a similar mechanism of action". Why then does the appraisal process not consider results seen in patients being treated with nusinersen to gain a better indication of the longer-term efficacy of risdiplam? • Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? The nature of SMA means that appraisals for any new drug do not sit under NICE's standard appraisal route or their highly specialised technology route. The fact the ACD mentions that risdiplam would not meet NICE's criteria for cost-effectiveness even at zero cost to the NHS is a clear illustration of this. Therefore, patients are being discriminated against due the nature of the condition not slotting nicely into one of NICE's 2 appraisal routes. SMA sufferers have been badly let down by NICE's flawed appraisal process in the past (nusinersen) and they continue to be so. With nusinersen, NICE falsely represented that the drug would be "available for all" and subsequently backtracked on this statement. Additionally, NICE did not deliver their decision within documented, or indeed reasonable, timeframes. Nusinersen was approved by the European Medicines Agency on 1 June 2017. On 3 July 2019 (OVER TWO YEARS LATER) the managed access agreement was published (and it is worth noting at this point that most eligible adult patients still can't access nusinersen due to inefficiencies in the NHS). Four years after the medication was approved, SMA patients (who are deteriorating physically every single day – SMA doesn't wait for bureaucracy to take its course) are still waiting. With risdiplam, NICE has the opportunity to partly atone for the appalling manner in which SMA patients were treated under the nusinersen appraisal. Yet NICE's initial stance is to decline SMA patients access to this innovative and much-needed medication! You will therefore understand why the committee's negative decision will be regarded by all those affected by SMA as particularly cruel.	
45			• Has all of the relevant evidence been taken into account? No because because Evrysdi does the same job as Spinraza and if Spinraza is available then I think Evrysdi should also be available. Evrysdi is available in lot of other countries and people who are using it finding it effective. I hope NICE will show bit more compassion and allow this drug because SMA is a devastating condition and for people with SMA every day is a hell. I am talking from personal experience because I suffer from SMA Type 3 and every night when I go to sleep I wish I never wake up again.	Thank you for your comments. Risdiplam has been recommended as part of a managed access agreement.

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			• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No because it is cheaper than Spinraza and can be administered at home. No need for the hospital visits or the need for the specialist to administer the drug so there will be savings there. • Are the recommendations sound and a suitable basis for guidance to the NHS? I feel NICE should consider from the perspective of SMA patients and try help out whatever way possible. • Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Since Spinraza is not suitable for everyone because some people had their spines fused or for other reasons, I feel those people will feel being discriminated against because how come some people with the same condition can receive the treatment and others can't. Totally unfair. Based on the facts that Evrysdi is suitable for vast majority of SMA patients, is cheaper than Spinraza, does the same job as Spinraza and can be administered at home, I feel this drug should definitely be available. Also, it will be even more effective when Scholar Rock comes out, which should also be made available. I feel for some of us with SMA, Evrysdi is the only hope so please don't deny us this treatment. I hope committee members and people who have the power to make decisions will show utmost compassion when making their final decision and will also put themselves in our shoes and feel what it's like to live with this debilitating condition and have to depend on others day and night.	
46			• Has all of the relevant evidence been taken into account? No: The committee acknowledges that the present classification of SMA is not a suitable one for appraising treatment. • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No: The clinical effectiveness of the drug does not give enough weight to its ability to halt the progress of the condition. Nor its ability to subtly improve breathing and fine motor skills. The cost effectiveness of the drug is greater than stated. For example a carer who sacrifices a nursing career at degree level is a cost to society as a whole and a cost to the family. A carer who becomes unwell becomes an additional burden on the state.	Thank you for your comments. Risdiplam has been recommended as part of a managed access agreement.

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			SMA patients can be net contributors to the state who may gradually lose the ability to contribute. • Are the recommendations sound and a suitable basis for guidance to the NHS? No. • Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? No. • Section 2.3: “The list price is £7,900 per 60mg/80ml vial. The company has a commercial arrangement, which would have applied if the technology had been recommended.” It is difficult to comment on an unspecified 'commercial arrangement' • Section 3.12: “It concluded that the company's utility gain for fine motor skills is acceptable but there is uncertainty around the exact value and the benefit could be larger.” Agreed. • Section 3.2: “The committee acknowledged the limitations of the current SMA classification system but concluded that it had been used in the marketing authorisation and clinical evidence for risdiplam.” If the committee is to pursue clinical excellence should it not advise on a better classification? • Section 3.3: “The committee concluded that SMA has a substantial effect on the quality of life of patients, caregivers and their families.” Has this been taken into account when determining the value of a QALY? • Section 3.11: “In the absence of updated criteria from TA588, the committee concluded that the company's stopping rules may not be appropriate and it would like to see stopping rules based on clinical criteria that have been agreed with clinical and patient experts.”	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Agreed.	
47			• Has all of the relevant evidence been taken into account? It is unlikely that a member of the general public is qualified to answer this question. I am answering the questions a keen follower of progress in treatment of SMA for nearly 18years. Our family know the true physical, emotional and health and financial costs of living and caring for a family member with SMA. Every family's experience is unique and therefore relevant evidence is broad and comparisons difficult to draw. The most relevant evidence to me is that this treatment can be given orally, crosses the blood brain barrier and also is present in the general circulatory system. At the very least it can halt the progressing of SMA and in some cases improve motor function. It also seems that it is more effective at preventing the deterioration in breathing and ability to swallow. Which at this time is of paramount importance to our family. Having been diagnosed with type 3 SMA we never thought that we would have to witness SMA taking so much from our grandchild. • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? I believe that cost effectiveness is indescribably difficult to quantify and too much of the decision has been based on the economic modelling of QUALY's and ICER's, which the evidence points out is an inadequate method of measuring impact. How can these models express the fear of being unable to breath or eat without chocking, being unable to lift a drink, dress yourself, turn in bed, use the bathroom unaided, have personal privacy put into the hands of strangers? How can QUALY'S AND ICER's express the loss of a professional career to become a parent carer or the lack of progression in a career for a carer due to the commitment needed to give exceptional care to a member of the family? What is the value of coping with the difficulty of organising a holiday, visiting friends and family, having an evening out as a couple? The loss of a retirement for grandparents as they willingly divert their energy to supporting families affected by SMA? These things cannot be given a monetary value. What is the value given to the relentless form filling ensuring systems are in place, fighting for your child's rights and care needs? None of these can be quantified. In the evidence it was agreed that the cost benefits analysis should be against Best Standard Care. It is proven this only gives care and does not reverse or halt the progression of SMA. I do not believe that in the present circumstances this is a reasonable comparison. Now there are two treatments approved, the comparison should be between the effectiveness, accessibility and clinical outcomes of treatments, in the various scenarios of SMA, which as stated in the evidence are inadequately classified. The choice of treatment should be at the discretion of the lead clinical team. They have the information available about the clinical condition of the patient, the efficacy of the available treatments and can assess the progression of SMA and prescribe the appropriate treatment. Whilst treatment is ongoing, they are in the best position to evaluate the success / failure of	Thank you for your comments. Risdiplam has been recommended as part of a managed access agreement.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			the chosen treatment. The addition of Risdiplam adds to a suite of treatments available to clinicians. This could mean that the most suitable treatment is selected for individual patients. It should therefore not add to the cost of treating individual SMA patients because treatments will not run concurrently. It has already been decide that all patients who have SMA should receive treatment under the MAA and this should be implemented within a year, Having competition also drives down costs and increases competition for further innovation and cost reduction. The addition of Risdiplam will speed up rollout which has been significantly adversely affected by COVID restrictions on in patient care. In the last few years two treatments have been approved by NICE expensive but both may completely alter the course of SMA. Yet the cost of Risdiplam has been compared with Best Standard Care. Recently NICE gave approval for all patients with SMA to be treated with Spinraza. An acknowledgement that walking is not an endpoint that all will achieve and there are other factors which needing treatment. I am profoundly grateful for this, but we know Spinraza may not be suitable for all and Risdiplam could be a solution to the problems of access to be treated with Spinraza or Zolgensma. I should like to highlight some of these costs when compared with Spinraza which have not been considered in the evidence. 1 Loss of workdays for parents/ carers taking the SMA patient for treatment. 2 Loss of school or work days for the SMA patient, 3 Cost of travel to the treatment centre if Spinraza is the only treatment of choice. 4 Cost of the consultants and nurses giving the injection, in our case two consultants will be required because of spinal surgery. 5 Cost of radiology , and supporting staff 6 Risk of repeated radiology exposure. 7 The possibility of hospitalization after the intrathecal injection because of the distance travelled. So additional loss of time. If this treatment is given to younger children, whose symptom have not progressed, it could completely stop the inevitable progression of SMA. Some of the benefits could be. 1 No need for spinal fusion 2 No need for wheelchairs. 3 Reduction in physiotherapist and occupational therapist time 4 Reduction in home adaptations with the associated cost to social services. 5 Cost of external care givers stop • Are the recommendations sound and a suitable basis for guidance to the NHS?	

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			I do not believe that the cost effectiveness of a treatment, in a civilised developed society, should guide its use, if it is shown to give benefits to those desperately needing treatment. • Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? I think that the whole debate around SMA treatment. past and present, emphasises on motor milestones, lack of or loss of them. and taken little time to consider the fact that SMA patients are articulate, usually have above average/high IQ and have 'feelings' . They have to work harder than the general population to reach their educational potential as they have spent many hours having physiotherapy, hospital visits for assessments, dealing with colds which turn into major chest infections . Yet despite this they just push on to catch up on lost time. Not once have I read any document which takes into account that people with SMA are just like you and me. They are identified only by their disability not their other abilities. This is a continuing and worrying thread. It is with great sadness and dismay that the committee have recommended refusal of this innovative treatment for all types of SMA, • Section 1.2: “SMA is a rare genetic condition and there is an unmet need for effective treatments that could slow disease progression.” “SMA is a rare genetic condition and there is an unmet need for effective treatments that could slow disease progression.” The committee recognises that there is a need for treatment of this devastating condition. This need is urgent. People and families living with SMA know the course of the disease is progressive and relentless, choose how high the Best Standard of Care available to them. The progression of SMA leads to the loss of so many abilities, the most devesting result is death. Living with SMA often leads to inability to breath, chew and swallow without assistance, besides removing most motor functions. The people living with SMA have, usually, normal or above normal intelligence and with Best Standard of Care, go to mainstream school, university and follow this with productive and fulfilling lives. SMA strips them of their physical abilities and the prospect of becoming a person who contributes to Society is significantly diminished. Treatment is urgently required to help them reach their full potential. That treatment is available.	

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			• Section 1.2: “There is no evidence on risdiplam for babies with pre-symptomatic SMA. Clinical evidence shows that risdiplam improves motor function in SMA types 1 to 3. Also, there is some evidence suggesting that people with type 1 SMA who have risdiplam live for longer. But there is no direct evidence comparing risdiplam with best supportive care for type 1 SMA. And there is no long-term evidence, so the estimated long-term benefits are highly uncertain.” Surely this is obvious, they have yet to display symptoms so why would there be any evidence or reason to treat. These children will not be identified until screening for the condition at birth for all babies, Very few babies may be identified if they are younger siblings of children diagnosed with SMA. This is a very low number of the SMA population in the world so difficult to identify and form into a study. One of the problems for people born with SMA is that their symptoms may not be apparent for several months or years after they are born. Even then the pathway to diagnosis is not smooth with long waits for a diagnosis and often an erroneous diagnosis before the correct diagnosis is made. "Also, there is some evidence suggesting that people with type 1 SMA who have Risdiplam live for longer. But there is no direct evidence comparing Risdiplam with Best Supportive Care for type 1 SMA." The most recent evidence on Type 1 SMA, treated with Risdiplam, (Roche virtual event on Key Evrysdi presented at the 2021 CureSMA Annual Meeting 14th June 2021) shows significant gain in motor milestones after 12months of treatment. The milestones reached were compared with WHO milestone achievements and are similar to the world population . "there is no long-term evidence, so the estimated long-term benefits are highly uncertain." It will not be know whether improvement will continue unless they continue to receive the treatment. We know that the outcome of Best Supportive Care will be little or no gain in motor function and untimely death. Treating SMA now is 'buying time' for future treatments, which may cost less and have greater effect. • Section 1.2: “The committee considered a wide range of issues in its decision-making. In particular, it discussed the rarity and severity of SMA, risdiplam's innovative oral administration, uncertainties in the evidence, and whether risdiplam should be considered as an end-of-life treatment.” "In particular, it discussed the rarity and severity of SMA, risdiplam's innovative oral administration" The oral administration of Risdiplam, makes it accessible to a larger group of people with SMA. There are several factors which make the administration of Risdiplam preferable to Spinraza. a Those who have had spinal fusion making intrathecal delivery difficult or impossible. b Those who live far from centres licenced to deliver Spinraza. c The complexity of delivery of Spinraza needing highly skilled doctors and technicians. d Theatre and X-ray time , which could be utilised for other urgent purposes. e The complications which can occur from intrathecal delivery.	

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			f Time lost from education and work of both the SMA patient and the carer / PA. g The circulation of the medication in the CNS and the general circulation make this treatment particularly appealing for in people who have swallowing and breathing difficulties . I understand Spinraza only circulates only in the CNS and improves motor function. "whether Risdiplam should be considered as an end-of-life treatment." I am assuming that this refers to babies with SMA type 1, who are now being given the gene therapy Zolgensma. This treatment only is available to babies under the year of 1. There are therefore babies, with SMA type 1, who are predicted to die before the age of 2. These babies currently are not going to have this treatment but may be having Spinraza. It should not be thought that the lives of these children is over if a treatment is available. I would consider both Risdiplam and Spinraza as "beginning of life" treatment for people with SMA of all types older than 1. • Section 1.2: “The cost-effectiveness estimates presented are much higher than what NICE usually considers an acceptable use of NHS resources. So, even taking these other factors into account, risdiplam cannot currently be recommended.” The UK is the Worlds 5th largest economy. Let us not dither over cost. How can we let people live with this devastating condition, which affect all walks of life, whole extended families, as well as the people living with SMA. It comes to families uninvited. Treatments are required now, our family has waited 18 years for this, many families for much much longer. NICE have mechanisms (MAA) for accepting drugs with cost higher then normally considered. Risdiplam is an additional treatment in the armoury for SMA and will not be used concurrently with the treatments already approved. So unless the costs are significantly different to Spinraza should this be an issue? Excluding one treatment, of two available, creating a monopoly for the other treatment. • Section 2.1 “Risdiplam (Evrysdi, Roche) is indicated for 'the treatment of 5q spinal muscular atrophy (SMA) in patients 2 months of age and older, with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies'." Risdiplam is already licenced under the EAMS pathway by the MHRA. Why can this access not be opened to all people with SMA who have a clinical need. Is this just a cost issue because the treatment appears to be having a positive effect?” • Section 2.2 "The list price is £7,900 per 60mg/80ml vial. The company has a commercial arrangement, which would	

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			have applied if the technology had been recommended." The actual pricing of Spinraza and Risdiplam to the NHS is redacted in the documents as ' consumers' we cannot know whether the two treatments are of a comparable price. It is up to the negotiators to finalise an equitable cost of the treatment. Having read all the documents I am assuming that cost is a key barrier to the committees approval. • Section 3 "The company's unanchored matched adjusted indirect comparison of Risdiplam with best supportive care is acceptable. " Other treatments are now available. It is known that Best Supportive Care leads only to deterioration. The cost and standards of BSC vary widely would it not now be more appropriate to compare with the other treatments in use. Particularly in reference to method of delivery of the treatment and the possible more beneficial outcomes on breathing and swallowing, a particular concern of SMA patients who have already lost a significant amount of mobility and muscle function. • Section 3.12 "The patient experts described the importance of maintaining upper limb function because it allows independence. They explained that some benefits were not captured in the available motor function scales because even small improvements were highly valued by patients and made a large difference to health-related quality of life." Until treatment is available to the wider SMA community we will not find out. What is certain is that these skills will be lost in some patients with advanced motor deterioration. They should be given a chance at maintaining their function. • Section 3.12: “The patient experts described the importance of maintaining upper limb function because it allows independence.” This is SO important to members of the SMA community. The importance cannot be emphasised enough. It is the difference between feeding and washing yourself. Using the WC and showering independently, even though you are using a hoist to facilitate this. Writing drawing, baking, using the wheelchair controls are all dependent on upper body and fine motor skills. Brushing teeth, opening packets cutting up food the list goes on. It is these small things, which they face losing, and keep the SMA community fighting for treatment.	

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			• Section 3.13 " The committee concluded that the ERG's approach to including caregiver utility values is consistent with TA588 but neither the company's nor the ERG approach is ideal, so there is substantial uncertainty" I agree with the uncertainty of including care giver utility values. How can QUALY'S AND ICER's express the loss of a professional career to become a parent carer or the lack of progression in a career for a carer due to the commitment needed to give exceptional care to a member of the family? What is the value of coping with the difficulty of organising a holiday, visiting friends and family, having an evening out as a couple? The loss of a retirement for grandparents as they willingly divert their energy to supporting families affected by SMA? Living without a second carer due to the dangers of infecting with COVID to the household. Living with the fear of being ill yourself and unable to care. These things cannot be given a monetary value. What is the value given to the relentless form filling ensuring systems are in place, fighting for your child's rights and care needs? None of these can be quantified. • Section 3 "The patient experts explained that SMA is a progressive disorder so all patients will experience more severe symptoms over time. " The treatment of the symptoms of SMA should be decided by need evaluated by the clinical team. Not the type as is currently defined. • Section 3.1 The generalised description of the symptoms and severity of SMA are difficult to use in practice. The manifestations of SMA have to be dealt with as they present in the individual and cannot only be defined by type . Treatment should not be confined to type , it should be by clinical need and they should have a choice of treatments available to them. . • Section 3.1 Type 3 SMA is defined as a 'milder' type of SMA this does not always follow. Some of Type 3 patients can develop very severe symptoms of SMA. Scoliosis - requiring surgery, not walking needing to use a motorised wheelchair, upper body weakness , breathing difficulty, swallowing difficulty etc. they can be affected by SMA the same as Type 2 , the symptoms just take longer to develop. Others develop only 'mild' symptoms and can walk propel themselves in a wheelchair, do transfers, sit themselves and undertake most daily functions for a longer period and retain upper body strength and control.	

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			This is not the fault of the clinicians misdiagnosing . It is a deficiency in the knowledge and understanding of how the disease progresses and what other factors are controlling this. For now there is the system of Type 1, 2 3 and 4, but it should not be a system which is used to give or refuse access to any treatment. Access should be available decided on patient symptoms by the clinical team. • Section 3.1 "The committee understood that risdiplam's marketing authorisation includes types 1 to 3 SMA as currently defined by the SMA classification system and these definitions were also used in the clinical evidence (see section 3.5). The committee acknowledged the limitations of the current SMA classification system but concluded that it had been used in the marketing authorisation and clinical evidence for risdiplam." It with great relief that the committee understand the limitations of classification and that this treatment, should it be authorised, should be available for all types of SMA according to clinical need. • Section 3.2 Every family living with SMA is different. Some families have two or three children with the condition. What is common the relentless progress of the condition choose how hard you try to minimise it . Having to fight the 'system' for support, adaptations and treatment. The interminable form filling to justify your family's particular needs. The anticipation of ' how bad can it get'. The financial worries as you have to give up work to care. The loss of your identify as you become ' the carer '. The juggling of family with children who are not ' disabled' . The negotiations with the education system as you wish your bright child to go to main stream school and university. The toll this all takes on your own physical health and wellbeing is immeasurable. • Section 3.3 In the evidence it was agreed that the cost benefits analysis should be against Best Standard Care. It is proven this only gives care and does not reverse or halt the progression of SMA. I do not believe that in the present circumstances this is a reasonable comparison. Now there are two alternative treatments approved, the comparison should be between the effectiveness, accessibility and clinical outcomes of the treatments, in the various scenarios of SMA, which as stated in the evidence are inadequately classified. The choice of treatment should be at the discretion of the lead clinical team. They have the information available about the clinical condition of the patient, the efficacy of the available treatments and can assess the progression of SMA and prescribe the appropriate treatment. Whilst treatment is ongoing, they are in the best position to evaluate the success / failure of the chosen treatment.	

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			• Section 3.5 If the clinical studies had shown that there was no meaningful gains from administering the treatment the drug company would not have submitted Risdiplam for approval. • Section 3.5 "The committee concluded that it had not seen any evidence for people who have had nusinersen and agreed to take this into account when making its recommendations" There are a group of TYPE 3 SMA patients who were denied accessibility to Nusinersen. Recently this decision was reversed. The delay of receiving treatment has been compounded by COVID restrictions. During the delay of almost 2years their mobility and strength has deteriorated . These patients are desperate to receive a treatment. They are generally older, understand completely the implications of the progressive nature of the condition. Many of these patients will have had spinal fusion for scoliosis and access to give intrathecal injection will be complex, difficult and is some cases impossible. these people need an alternative route of administration of treatment. Risdiplam gives this option and would speed up treatment, without the significant strain on the NHS of administering Spinraza . • Section 3.7 "The committee concluded that it had not seen any evidence for people who had pre-symptomatic SMA and agreed to take this into account when making its recommendations. " Until there is genetic testing at birth for SMA there will only be a few children who are diagnosed pre - symptomatically with SMA . Only children with older siblings, with a diagnosis of SMA , are screened. Therefore the number of known pre-symptomatic children will be small. Pre-symptomatic diagnosis of adults would require whole population screening and therefore the accumulation of evidence in pre symptomatic groups is unlikely to be currently obtained. • Section 3.8 Improvements in motor function would be welcome but we are aware stabilization of symptoms at this point is a realistic expectation for some patients who have significant deterioration of motor movement.. This would give great comfort to those who are having or facing difficulties with breathing speaking and swallowing. • Section 3.9: “The committee concluded that, although risdiplam would likely provide long-term benefits, the size and nature of these benefits are not known so this is uncertain.”	

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			People with SMA should have the opportunity to explore what the long term benefits may be. They know the course of SMA if no treatment is given. • Section 3.11 It would seem fair that the stopping rule is based on the clinical criteria and is the subject for discussion with ethic committee, the clinical team, the patient and their family. There are already a number of conditions which are 'untreatable' this type of decision has to be made by the clinician and the patient. It should not be a reason for withholding treatment in the first place. • Section 3.15 By treating with either Spinraza or Risdiplam . We are 'buying time' for more treatments to be developed and authorised. In the course of the preparation of application, to NICE, for Risdiplam to be authorised as a treatment for SMA, a gene therapy , Zolgensma, has been authorised, in the UK, for type 1 SMA patients. This is may be a game changer and in the future we may not see any people needing any other treatment. There will be more of these game changers under development but for now we just have two possibilities for people over the age of one. These should not be denied to the SMA community. • Section 3.16: “The committee noted that, using its preferred assumptions, the most plausible ICER for type 1 SMA was much higher than £50,000 per QALY gained. For types 2 and 3 the ICER was much higher than £30,000 per QALY gained (the company considers the ICERs to be confidential so they cannot be reported here). The committee concluded that the ICERs for risdiplam are above £50,000 per QALY gained.” The clinical effectiveness of Risdiplam, albeit to stabilise, not cure, gives such hope. HOPE is a word not used in the household of families with SMA , vocabulary often. Hope that they will not choke whilst sharing a meal . Hope that they will not be admitted to hospital with chest infections. Hope they will not need night-time ventilation. Hope their mother (as it usually is) will get a full night’s sleep. Hope that they will successfully attend University. Hope that they will be a sharing and contributing member of Society, able to visit friends’ homes and navigate the inaccessible world Society has created. These are just a small example of things this treatment gives SMA families hope for. If treatments are not approved all this hope for many families is diminished. I believe that cost effectiveness is indescribably difficult to quantify and too much of the decision has been based on the economic modelling of QUALY's and ICER's, which the evidence points out is an inadequate method of measuring impact. How can these models express the fear of being unable to	

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			breath or eat without chocking, being unable to lift a drink, dress yourself, turn in bed, use the bathroom unaided, have personal privacy put into the hands of strangers? • Section 3.18: “The clinical and patient experts agreed that an alternative treatment option is needed. The committee concluded that risdiplam is innovative, but no data had been presented for benefits relating to its innovative nature that had not already been captured in the economic analyses.” In the last few years two treatments have been approved by NICE expensive but both may completely alter the course of SMA. Yet the cost of Risdiplam has been compared with Best Standard Care. Recently NICE gave approval for all patients with SMA to be treated with Spinraza. An acknowledgement that walking is not an endpoint that all will achieve and there are other factors which needing treatment. I am profoundly grateful for this, but we know Spinraza may not be suitable for all and Risdiplam could be a solution to the problems of access to be treatment. I should like to highlight some of these costs when compared with Spinraza which have not been considered in the evidence. 1 Loss of workdays for parents/ carers taking the SMA patient for treatment. 2 Loss of school or work days for the SMA patient, 3 Cost of travel to the treatment centre if Spinraza is the only treatment of choice. 4 Cost of the consultants and nurses giving the injection, in our case two consultants will be required because of spinal surgery. 5 Cost of radiology , and supporting staff 6 Risk of repeated radiology exposure. 7 The possibility of hospitalization after the intrathecal injection because of the distance travelled. So additional loss of time. If this treatment is given to younger children, whose symptom have not progressed, it could completely stop the inevitable progression of SMA. Some of the benefits could be. 1 No need for spinal fusion 2 No need for wheelchairs. 3 Reduction in physiotherapist and occupational therapist time 4 Reduction in home adaptations with the associated cost to social services. 5 Cost of external care givers stop • Section 3.20: “The committee acknowledged that the population eligible for risdiplam has serious disabilities. It acknowledged and considered the nature of the eligible population as part of its decision making.”	

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			So what is the reason for refusing approval of Risdiplam ? Cost? If so why can the drug not be approved using a MAA? • Section 3.21: “It acknowledged and considered whether any adjustments to its normal considerations were needed to take into account the rarity and severity of the disease. The decision making takes into account the rarity and severity of the disease.” So why is treatment being denied? • Section 3.22: “The committee also acknowledged other factors including the innovative nature of risdiplam, the nature of the eligible population and the rarity and severity of SMA (see sections 3.18 to 3.21). Taking all this into account, the committee concluded that risdiplam is not likely to be a cost-effective use of NHS resources for treating SMA. It noted that the company had not submitted a proposal for a managed access agreement and concluded that risdiplam cannot be recommended for routine commissioning in the NHS at this time.” So, is the bottom line that this drug is not cost effective under the rule of £50,00 per QUALY? NICE have power under the MAA to authorise this treatment just as it has done for Spinraza. Having two treatments, which could be life changing, for people living with SMA is a bonus. It provides an option for treating clinical and social need. The treatments are both high cost but denying one authorisation will not drive down the overall cost of treating SMA. Approving Risdiplam will free up hospital space to treat some of the huge waiting list for many illnesses and conditions of people who can only receive their treatment in a clinical setting. Having treatment available to use at home, at the discretion of the clinical team, will speed up the rollout of this vital treatment. It will also avoid any delays to treatment which may be caused by another wave of COVID overwhelming our NHS.	

NICE National Institute for Health and Care Excellence

Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

Consultation on the appraisal consultation document – deadline for comments by 5pm on **Wednesday 23 June 2021.** To be submitted via NICE DOCS.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Roche UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

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1	**Introduction** Roche appreciates the opportunity to provide comments on the NICE Appraisal Consultation Document (ACD) for risdiplam for treating spinal muscular atrophy (SMA) [ID1631]. Roche is dedicated to finding solutions in collaboration with NICE for the concerns raised within the ACD such that risdiplam may be considered for a positive recommendation for use within the NHS. Despite existing treatment options, the unmet need remains high in this highly disabling disease area for a treatment that is able to: • Delay disease progression and maintain patients' existing motor abilities so they can continue to live their normal daily lives; • Improve or maintain essential bodily functions including the ability to breathe (respiratory function), swallow, vocalise and verbally communicate, as well as delay or prevent significant damage to the spine (scoliosis); • Increase patient survival such that they are able to spend more time with family, friends and loved ones. Moreover, this unmet need is further illustrated by the ongoing risdiplam Early Access to Medicines Scheme, in which over 200 patients have been enrolled so far. Rationale is provided in the comments below for instances where Roche would like to encourage the Committee to reconsider its conclusions. Roche has also submitted an appendix containing additional cost-effectiveness data to provide further support for the model assumptions. This response covers the following key points, addressing the concerns raised in the ACD: • Long-term follow-up from the SUNFISH and FIREFISH trials (24-month data) • Risdiplam treatment in pre-symptomatic patients and previously treated patients • Revised discontinuation criteria for risdiplam • Upper limb function utility for patients and carers • Alternative approach to modelling carer disutility • Bulbar function, respiratory and scoliosis patient disutilities and costs The revisions outlined below change the incremental cost-effectiveness ratio (ICERs) to £[redacted] for type 2/3 SMA and between £[redacted] and £[redacted] for type 1 SMA. Roche acknowledges that a range of ICERs are not usually presented in the base-case, however modelling approaches face particular challenges in type 1 SMA, such as the effect of the extension to life achieved with risdiplam on carer quality-adjusted life years (QALYs), which Roche has attempted to address below. Additionally, challenges are posed through SMA being a highly expensive disease to treat, which requires care from multiple healthcare professionals and specialist equipment. Roche would like to highlight that whilst increasing survival does increase patient life years, it also increases costs and carer QALY losses, which are detrimental to the ICER of risdiplam In addition, Roche requests that the decision-modifiers taken into account for the appraisal of nusinersen are also applied for risdiplam, given the rarity and highly disabling nature of the disease, the high mortality of people with SMA, many of whom are children, as well as the severe disease burden, which has wider societal impacts in terms of emotional and financial effects on people with SMA and their families.

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	As noted above, Roche feels strongly that risdiplam can address a significant unmet need for an effective treatment for SMA patients in the UK, and wishes to note that the ICERs presented herein - following the revisions requested by the committee and inclusion of longer-term clinical data - are substantially lower than those reviewed at the first Appraisal Committee Meeting. Roche is committed to enabling people with SMA to gain access to risdiplam and is open and willing to continue collaboration as needed with NICE and NHS England to enable this to happen.
2	**<u>Long-term follow-up from the SUNFISH and FIREFISH trials (24-months data)</u>** Additional clinical data from the 24-month data cut of the trials investigating the effect of risdiplam on type 2/3 (SUNFISH trial) and type 1 (FIREFISH trial) SMA patients has become available since the original company submission. Results from the 24-month data cut of the SUNFISH trial demonstrate the continued efficacy of risdiplam, with further improvements in key endpoints recorded in comparison to the 12-month data, which informed the original company submission. Specifically, the following clinical results were obtained at the 24-month data time point:[1] • The mean change in 32-item Motor Function Measure (MFM-32) total score from baseline increased from 1.65 at 12 months to 1.83 at 24 months. • The upper limb function measured by the mean change in the Revised Upper Limb Module (RULM) total score further improved from 1.91 at 12 months to 2.79 at 24 months. • The mean change in the Expanded Hammersmith Functional Motor Scale – Expanded (HFMSE) total score also improved from 1.81 at 12 months to 2.15 at 24 months. • The patient-reported SMA Independence Scale (SMAIS) mean change was maintained at a similar score from baseline (0.95 at 12 months, 0.82 at 24 months), while the mean change in carer-reported SMAIS scores from baseline improved from 1.68 at 12 months to 2.73 at 24 months. These data demonstrate that risdiplam continues to have a beneficial impact on patients' motor abilities (as shown through MFM-32 and HFMSE scores) in addition to upper limb function (as demonstrated by the RULM scores). As supported by the SMAIS scores, these improvements enable patients to maintain their independence and quality of life (QoL). The 24-month data have been incorporated into the type 2/3 model so that it is informed by longer-term efficacy data for risdiplam. The FIREFISH 24-month data also demonstrate the continued efficacy of risdiplam in comparison to the 12-month data cut. Specifically, the following clinical results were obtained at the 24-months data time point:[2] • The proportion of patients sitting without support for 5 seconds (using the Bayley Scales of Infant and Toddler Development, Third edition [BSID-III] measure) increased from 29% (at 12 months) to 61% (at 24 months). • The proportion of patients who achieved a score of 40 or higher in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) increased from 56% (at 12 months) to 76% (at 24 months). • Similarly, the proportion of motor milestone responders as assessed by the Hammersmith Infant Neurological Examination, Module 2 (HINE-2) measure increased from 78% (at 12 months) to 85% (at 24 months). The proportion of patients able to support their weight or stand with support, as assessed by HINE-2, increased from 22% to 27% from 12 months to 24 months. While assessing the walking item of HINE-2, the proportion of patients that were able to bounce were also recorded, and this increased from 2% at month 12 to 4% at month 24. • The proportion of patients alive (across with and without permanent ventilation) remained high

	at 83% at 24 months. • The proportion of patients that were able to feed orally was maintained at a high level (83% at month 12 and 85% at month 24). These data demonstrate that risdiplam continues to have a beneficial impact on the motor abilities of type 1 SMA patients (as shown through BSID-III, CHOP-INTEND and HINE-2 scores). As noted by the Committee in the ACD, type 1 SMA patients on BSC typically die within 2 years if they do not receive respiratory support.[3] In FIREFISH, 83% of patients that do not receive permanent ventilation were alive at the 24-month data cut. Therefore, risdiplam extends life for type 1 SMA patients, as well as enabling them to maintain or improve their QoL, through improved motor function and the ability to feed orally. The 24-month data have been incorporated into the type 1 model so that it is informed by longer-term efficacy data for risdiplam.
3	**Risdiplam treatment in pre-symptomatic patients** ***RAINBOWFISH clinical evidence*** The open-label Phase II study (RAINBOWFISH, NCT03779334[4]), investigating the efficacy and safety of risdiplam in infants with genetically diagnosed and presymptomatic SMA is currently recruiting. Preliminary data were presented at the Cure SMA Virtual Research & Clinical Care Meeting (June 7–11, 2021).[5] RAINBOWFISH (NCT03779334) is a multicentre, open-label, single-arm, study to investigate efficacy, safety and pharmacokinetics (PK)/pharmacodynamics (PD) of risdiplam in infants with genetically diagnosed presymptomatic SMA. RAINBOWFISH is actively enrolling infants aged from birth to 6 weeks (at first dose), regardless of *SMN2* copy number. Infants will receive risdiplam for 24 months, followed by a 36-month extension. Primary analyses will be conducted at 12 months of treatment in infants with two *SMN2* copies and compound muscle action potential (CMAP) amplitude ≥1.5 mV at baseline. The primary endpoint is the proportion of these infants sitting without support for ≥5 seconds after 12 months of treatment (assessed by Item 22 of the Gross Motor Scale of the Bayley Scales of Infant and Toddler Development, Third Edition). Secondary endpoints include the development of clinically manifested SMA, survival and permanent ventilation, achievement of motor milestones, motor function, growth measures, nutritional status, CMAP, PK and safety monitoring. For the first 12 enrolled infants, the median age at first dose was 28.5 days (range: 16–40 days). SMN protein data are currently available for nine of these infants. The mean baseline SMN protein level in blood prior to risdiplam treatment was 5.8 ng/mL, which was higher than the mean baseline SMN protein levels in patients in the FIREFISH (type 1 SMA patients; 2.7 ng/mL) and SUNFISH (type 2/3 SMA patients, 3.4 ng/mL) studies of risdiplam. Enrolled infants have been treated with risdiplam for a median of 7.4 months (range: 1.1–18.1 months). Five infants have been treated for ≥12 months (preliminary efficacy data are available for these infants) and includes two infants with two *SMN2* copies and three infants with >2 *SMN2* copies. Three infants have been treated for ≥6 to <12 months, and five infants treated for <6 months. Infants treated with risdiplam for at least 12 months (n=5) reached near maximum CHOP-INTEND scores by 4–5 months of age. At 4 months of treatment, 4/5 infants (80%) scored ≥60, 1/5 infants (20%) scored 58. At 12 months of treatment, 5/5 infants (100%) scored ≥60; 4/5 infants (80%) scored the maximum CHOP-INTEND score of 64 (including both infants with two *SMN2* copies), with the remaining 1/5 infant (20%) scoring 63 with a subsequent score of 64. Infants treated with risdiplam for at least 12 months (n=5) achieved Hammersmith Infant Neurological Examination, Section 2 (HINE-2) motor milestones; at the 20th February 2021 data cut-off, 80% of infants

	(4/5) scored the maximum HINE-2 score of 26; this includes one infant with two *SMN2* copies, one infant with two *SMN2* copies had a HINE-2 total score of 23. This means that head control, sitting, rolling, and crawling milestones were achieved in all five babies; four (80%) were able to stand unaided and walk independently, with one baby standing with support and one bouncing. Most of the infants treated for at least 12 months achieved motor milestones within the World Health Organisation Multicentre Growth Reference study group (WHOGRS) windows for healthy children. No treatment-related serious adverse events were reported in pre-symptomatic infants treated with risdiplam for up to 18.1 months; adverse events were more reflective of the age of the infants rather than the underlying SMA (nasal congestion reported in four babies (33%), cough, teething and vomiting reported in three babies (25%), and two babies each reporting eczema, abdominal pain, diarrhoea, gastroenteritis, papulae and pyrexia (17%)). When this is compared with the natural history of type 1 SMA, these data are remarkable. The ANCHOVY study was a global, multicentre, chart review study that provided an update on natural history data in patients with type 1 SMA from a broad geographical area[6]. Patient data (n=60) were extracted from medical records from sites in Belgium (n=5), Brazil (n=6), Croatia (n=3), France (n=10), Italy (n=10), Japan (n=7), Poland (n=4), Russia (n=8) and the USA (n=7). Thirty cases (50%) had confirmed *SMN2* copy number (the remaining 30 (50%) patients the *SMN2* copy number was unknown). Among the patients who had data, no patients achieved any level of sitting or head control after 9 months of age. One patient (two *SMN2* copies) was able to sit with support at 9 months of age, eight patients achieved the head control item "wobbles" (four patients had two copies of *SMN2*, four patients had unknown *SMN2* copies) at some time up to 9 months of age, one patient (unknown *SMN2* copies) was able to maintain upright head control at 6 months of age. No patients were able to sit without support. By 12 months of age, no HINE-2 motor milestones were achieved for rolling, voluntary grasp and kicking, and no patients achieved any level of crawling, standing or walking. These results illustrate clear and clinically meaningful improvements of risdiplam-treated patients in the RAINBOWFISH study compared to SMA patients observed in the ANCHOVY study. Roche therefore request that the Committee considers this evidence in their decision-making for use of risdiplam in pre-symptomatic SMA patients.
4	**<u>Risdiplam treatment in previously treated patients</u>** ***JEWELFISH clinical evidence*** There is a growing body of evidence to support the use of risdiplam in people who have previously received alternative SMA therapy. JEWELFISH (NCT03032172) is a multi-centre, exploratory, non-comparative, open-label study investigating the safety, tolerability, PK and PK/PD relationship of risdiplam in adults, children and infants (aged 6 months to 60 years, n=174) with SMA who have previously been treated with other disease-modifying treatments.[7] The enrolled population included a broad range of ages (1–60 years), SMA types (1–3), *SMN2* copy numbers (1–4) and motor function (non-sitters, sitters and walkers). One patient withdrew from the study at baseline; of the remaining patients, 13 previously received RG7800, 76 received nusinersen (three patients in the nusinersen group had also received olesoxime previously), 70 received olesoxime and 14 received onasemnogene abeparvovec (AVXS-101; one patient in the onasemnogene abeparvovec group received treatment with onasemnogene abeparvovec first followed by nusinersen).[8] All patients had at least a 90-day period between the last dose of treatment and JEWELFISH screening. Risdiplam treatment led to a rapid and sustained, >2-fold increase in SMN protein levels compared with baseline levels in patients previously treated with nusinersen or onasemnogene abeparvovec[9], which was consistent with PD data from the SUNFISH study of treatment-naïve patients with Types 2/3 SMA. No

	drug-related safety findings leading to withdrawal were reported for any patient exposed to risdiplam in JEWELFISH. The safety profile of risdiplam was consistent with the safety profile observed in treatment-naïve patients. The JEWELFISH population is broad and heterogeneous, with a high degree of motor impairment at baseline, reflecting the real-world SMA population. Interim exploratory efficacy data demonstrated overall stabilisation in motor function at Month 12 in patients who began treatment with risdiplam following previous treatments. In a recent survey of 1474 people with SMA in Europe, >96% considered stabilisation of SMA important progress.[8] Of the 77 patients who previously received nusinersen, 24 patients (31%) reported treatment-related tolerability concerns relating to this treatment (challenges associated with intrathecal administration in patients with scoliosis or those who had undergone spinal surgery and were unable to receive a lumbar puncture); 14 patients (18%) cited lack of efficacy and eight patients (10%) loss of efficacy. Seven caregivers (9%) requested risdiplam treatment preferentially to nusinersen, and six patients (8%) cited patient preference as reason to enrol onto the JEWELFISH study. Other reasons were given in 18 cases (23%), and included treatment-related safety concerns, treatment reimbursement/insurance policy challenge, access infrastructure challenges (e.g. accessibility to hospital facilities), injection procedures, inconvenience of treatment, (or missing reason). This clearly demonstrates that some patients who have already had access to nusinersen are not able to receive continued nusinersen therapy for medical reasons. Patients in the JEWELFISH study previously treated with onasemnogene abeparvovec (n=14) cited hopes of additional benefit (n=8; 57%), caregiver preference (n=4; 29%), and treatment response (lack of efficacy, n=2; 14%) as the primary reason for enrolment into JEWELFISH. ***Experience within the risdiplam Early Access to Medicines Scheme (EAMS, MHRA EAMS Number: 00031/0011)*** Further evidence for use of risdiplam in previously treated patients is available from the Early Access to Medicines (EAMS) scheme. EAMS aims to give patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need. The risdiplam EAMS was approved for the following indication on the 17th September 2020: *Risdiplam is indicated for the treatment of patients 2 months of age and older with type 1 and type 2 spinal muscular atrophy (SMA) who are not suitable for authorised treatments.* Two hundred and three patients have been enrolled on the scheme so far, the oldest aged 69 years and the youngest less than one year of age. Type 2 patients represent the largest number of patients enrolled (n=180), with 23 type 1 patients enrolled into the scheme. Thirty patients had received previous treatment for SMA: three with olesoxime and 27 with nusinersen (two patients only received the first loading dose of nusinersen, one of these was unsuccessful); the additional patient was reported as receiving pre-treatment with salbutamol. Reasons for switching from nusinersen were documented to be scoliosis and spinal surgery impacting the ability to administer nusinersen intrathecally, despite some clinicians reporting use of general anaesthetic and interventional radiology. Adverse events and inability to tolerate nusinersen/IT administration was also recorded, with post-lumbar puncture vomiting and severe hypokalaemia reported for one patient each. One patient required tracheostomy whilst on nusinersen therapy so was unable to continue nusinersen due to the requirements of the managed access agreement.

Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

Consultation on the appraisal consultation document – deadline for comments by 5pm on **Wednesday 23 June 2021.** To be submitted via NICE DOCS.

	Clinical opinion Roche has consulted clinical experts (six neurologists and one physiotherapist) on whether they believe risdiplam would be effective in patients after a previous SMA therapy. Given its availability through a managed access agreement in the UK, the majority of clinical experience was based on switching from nusinersen. The clinical experts generally felt that risdiplam would be as effective as nusinersen, due to the similar mechanism of action, and that previously treated patients should therefore benefit from risdiplam.[10] One clinician mentioned that they had a few patients that switched from nusinersen to risdiplam and no health decline has been observed, and several reported improvements in bulbar and respiratory function.[10] Clinicians additionally emphasised that the oral route of administration for risdiplam is favourable.[10] In particular, clinicians have been keen to emphasise that the intrathecal administration of nusinersen is often a much more complex procedure than a typical intrathecal administration, such as for an oncology medicine. People requiring SMA therapy tend to have increasing degrees of scoliosis, which means continuous nusinersen administration over a number of years will become increasingly difficult. This raises further concern over exposure of patients to repeated X-rays/interventional radiology, and in addition, sedation (or general anaesthesia, if available in the centre) has associated risks that are exacerbated in a population that inherently has respiratory issues. In comparison, clinical experts positively commented on the oral route of administration for risdiplam, which may be administered at home, and noted that it may therefore be of interest to switch patients on nusinersen to risdiplam.[10] In the NHSE algorithm shown at the first Appraisal Committee Meeting, switching between nusinersen and risdiplam due to disease progression, patient choice, side effects, spinal access etc. was suggested as appropriate for a future patient pathway. Based on this pathway, Roche would like to ask the Committee to consider recommending risdiplam for previously treated patients, given the benefits that risdiplam would bring to this subgroup.
5	**<u>Revised discontinuation criteria for risdiplam</u>** Roche appreciates the criticism from the Evidence Review Group (ERG) that the time-based stopping rule submitted during technical engagement was not based on hard evidence, and understand the reasoning of the Committee that the stopping rules were not appropriate.[3] Roche has therefore included a stopping rule based on clinical criteria instead, in line with the ERG's recommendation. Based on guidance provided by the ERG on how a stopping rule may be best implemented in the models given their existing functionality, the following patient populations discontinue treatment with risdiplam at the time that they reach a 'plateau' in the updated models: • Type 2/3 SMA patients that have not reached the ability to sit unsupported [[redacted] % of type 2/3 patients] • Type 1 SMA patients that have not reached the ability sit [[redacted] % of type 1 patients]. The fact that so few risdiplam-treated patients discontinue at this timepoint reflects the high efficacy level of risdiplam and high proportions of patients in higher health states at this model timepoint. The rationale for selecting the timepoint at which patients 'plateau' is that at this timepoint no further improvement in motor milestone achievement is expected, and thus it may be assumed patients will not go on to achieve more advanced milestones in the future. NICE accepted in the ACD that a treatment-effect plateau of month 26 for type 2/3 SMA and month 66 for type 1 SMA is acceptable and consistent with NICE's technology appraisal of nusinersen.[3] Roche would like to highlight that aligning with the ERG's suggestion still reflects an outcome-based stopping rule, therefore putting considerable pressure on patients. Accordingly, Roche would like to emphasise that the discontinuation criteria are implemented in the models as a proxy for the purposes of Committee decision-making, and do not fully reflect how discontinuation criteria would be applied in

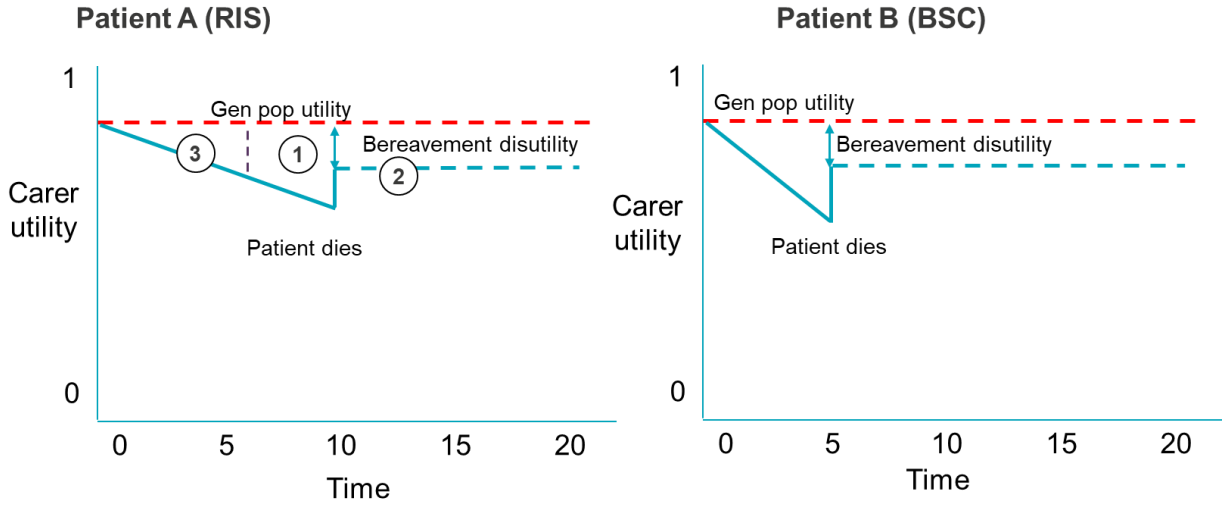
	clinical practice. Roche stresses that recently consulted clinicians felt strongly that the model approach should not be transferred to clinical practice.[10] If NICE chooses to impose an outcomes-based stopping rule on risdiplam, Roche requests that this aligns with the updated stopping rule for nusinersen. When deciding whether a patient should stop or continue treatment with nusinersen, the following criteria are considered by the treating clinician:[11] • Worsening of motor function • Requirement for permanent ventilation • Inability to administer the drug safely An additional stopping rule for type 3 SMA patients who lose ambulation after 12 months of treatment with nusinersen was recently removed.[11,12] Clinical experts consulted by Roche noted that the clinical guidance for risdiplam should reflect the guidance for nusinersen, as these are already established and clinicians appreciate consistency and are used to implementing them in clinical practice.[10]
6	**<u>Upper limb function utility</u>** As confirmed by patient experts during the first Appraisal Committee Meeting, the Committee noted that even small improvements in motor skills are highly valued by SMA patients, as they are important to maintain their independence, thereby making a substantial difference to the patients' QoL.[3] The Committee acknowledged during the first Appraisal Committee meeting that the SUNFISH trial showed improvements in upper limb function and SMAIS score at 12 months.[3] As mentioned above, the upper limb function measured by the mean change in RULM total score from baseline further improved from 1.91 at 12 months to 2.79 at 24 months.[1] Additionally, the mean change in patient-reported SMAIS was maintained at a similar score from baseline (0.95 at 12 months, 0.82 at 24 months), while the mean change in carer-reported SMAIS scores from baseline improved from 1.68 at 12 months to 2.73 at 24 months.[1] Therefore the 24-month data from SUNFISH further demonstrates the effect risdiplam has on maintaining or improving upper limb function and independence of SMA patients. In the ACD, the Committee noted that its preferred assumptions included a larger additional utility gain for fine motor skills than originally proposed by Roche at technical engagement, as some fine motor skills may not be captured in available motor function measures.[3] Roche subsequently consulted clinical and patient experts, who confirmed that the utility increase associated with upper limb function used in the technical engagement models are too low.[10] Several clinical and patient experts indicated that upper limb function improves a patient's QoL by ~50%.[10] The impact of upper limb function was emphasised by clinical and patient experts, who named the following examples of functions that patients without upper limb function would not be able to perform: ability to hold a drink and maintain hydration independently, ability to feed independently (open fridge, open bags, undo lids, chop up food, etc.), ability to move independently (access lifts, open doors, wheelchair control etc.), ability to write, control a computer mouse or a wheelchair joystick control, and the ability to scratch one's own nose.[10] One clinical expert commented that fatigue/stamina has an impact on a persons' upper limb function; he commented that nusinersen patients anecdotally refer to a decline in energy at the end of their 4-month dosing period. Continuous treatment with risdiplam should avoid this drop and personal accounts from several patients have endorsed this.[10] It is therefore clear that upper limb function has a substantial impact on patient's QoL, and as such should be accounted for in the cost-effectiveness models. Roche would like to note that, unfortunately, it is not straightforward to account for this increase in the models. Therefore, Roche has instead increased the patient utility associated with upper limb function to [redacted] in all health states where this had previously been applied during the technical engagement step (the "not sitting", "sitting with support" and "sitting without support" health states in the type 2/3 model, and the "not sitting" and "sitting" health states in the type 1 model). In addition, given the high levels of

	independence granted to people with SMA through upper limb function, as evidenced by feedback received from patients and carers,[10] a utility increment of 0.05 has been applied to caregivers in the risdiplam arm for the same aforementioned states in each model. As the effect that upper limb function can have on the QoL is stark according to clinical experts, patients and carers,[10] this estimate is highly likely to be conservative. Therefore, the models may still not fully reflect the clinical benefits of risdiplam. Accordingly, the company would like to request flexibility with regards to decision making.
7	**Alternative approach to modelling carer disutility** The company acknowledges the ERG's criticism that the additive approach to carer QALYs implicitly assumes that the carer either dies or survives with zero utility when the SMA patient dies, and results in the assumption that society places value on carers of surviving SMA patients but not on bereaved carers.[3] The company also agrees with the limitations of the ERG's approach to carer disutilities as highlighted by the Committee: the ICER increases as a result of subtracting substantial carer disutilities from the patient utility values, which themselves already reflect a poor QoL. As a result, the increased survival of risdiplam-treated patients results in a low number of QALYs at a high extra cost, particularly in the type 1 model. The Committee recognised the difficulties in valuing carer QoL in the ACD, noting that the "QALY loss" approach taken by the ERG has limitations, as it did not believe that including carer QoL would result in fewer carer QALYs when risdiplam extends survival of the patient.[3] Accordingly, Roche has explored alternative approaches to modelling carer QALYs that consider the following three key points: 1. Extension to patient life granted by risdiplam is of substantial value to carers. 2. The benefit of risdiplam to carers associated with delaying bereavement. 3. The QoL gained by carers through improved functional ability of the risdiplam-treated patients under their care. These three points are discussed further below: 1. It is the company's firm belief that the extension to life granted to patients by risdiplam is of substantial value to carers, who are very commonly family members of the patient. The company strongly do not believe that carers would trade-off caring for a patient for a longer period of time in favour of the patient experiencing an early death. As such, to reflect this, in the company's revised modelling approach, the ERG's original approach to modelling career disutility is adopted, however, carer QALY losses in the risdiplam arm associated specifically with extension to life over BSC have been disregarded from the analysis. This has been achieved through removing any further carer QALY losses associated with both risdiplam and BSC following the point of mean survival for the BSC arm in the model. The approach is in line with feedback from the Committee that they would like to see the impact of the analysis if carer disutility is no longer counted after death of the BSC patient. 2. As noted in the ACD, patient experts confirmed that bereavement would have a significant and sustained effect on carer QoL.[3] Therefore, a carer disutility for bereavement (-0.04 based on Song et al. [2010][13]) has been included, in line with the ERG's proposed approach at the first Appraisal Committee meeting. This QoL decrement has been applied from the point of mean survival in each treatment arm for the remaining time horizon, reflecting the extensive duration carers are likely to feel the loss of the patient. 3. As demonstrated by the clinical data, risdiplam results in functional gains in patients, which in turn enable patients to express a greater level of independence and reduces their dependence on the carer. Roche would therefore like to highlight to the Committee that the patients' functional gains resulting from risdiplam treatment also positively affect carers' QoL. This aspect was captured in

both the company's and ERG's original approach, and Roche has continued to capture this aspect in the updated models.

Roche's revised modelling approach summarising points 1–3 are represented on the graphs presented in Figure 1.

Figure 1. Illustration of company's revised approach to modelling carer disutility



Key: 1. Area indicated by '1' represents carer QALY losses associated with extension to life with risdiplam compared to BSC (disregarded from revised modelling approach); **2.** The disutility associated with bereavement is delayed through the extended life with risdiplam treatment compared to BSC (included in revised modelled approach); **3.** Reduced carer QALY losses with risdiplam treatment compared to BSC resulting from patients' functional gains (included in the original and revised modelling approach).
Footnote: Numbers on the graphs are arbitrary and for illustration only. The following assumptions are made: carer utility declines with time as patients' functional status worsens. Patients' functional status declines at a faster rate with BSC compared to risdiplam. Patients treated with BSC die at an earlier timepoint compared to risdiplam.
Abbreviations: BSC: best supportive care; Gen pop: general population; QALY: quality-adjusted life years; RIS: risdiplam

Despite the modelling approach for carer disutility described above resulting in reduced carer QALY losses per risdiplam patient compared to a BSC patient, carer QALYs in the risdiplam arm still accrue a greater negative total compared to the BSC arm in the base case. This is due to the fact that within the model cohort, a greater proportion of risdiplam patients are alive at any given point in the time horizon compared to BSC (until all patients have died). As such, a greater negative carer QALY loss is accumulated in total in the risdiplam arm compared to the BSC arm. Given this result remains contrary to the Committee's preference that including carer QoL should not result in the accumulation of fewer QALYs, an alternative analysis has also been presented for the Committee's consideration, in which a 'cap' has been applied to the total carer QALYs in the risdiplam arm for each health state, such that QALYs cannot exceed a more negative value than the BSC arm. This is more aligned with committee conclusions, however it is still a conservative approach as it assumes the caregiver quality of life is the same across the treatment arms. The ICER of this analysis is £[redacted] (please see appendix for further details).

As both of the above analyses are conservative, Roche felt it was important to highlight that when

	applying the additive approach to modelling caregiver QALYs, the ICER is £[redacted] (please see appendix for further details). Although Roche recognises the limitations of this approach, it is still a method encouraged by the NICE DSU on modelling caregiver QALYs, and highlights the impact the modelling has on the ICER. It is therefore plausible to consider that the true ICER lies within this range. Due to the approach to modelling carer QALYs being less problematic in the type 2/3 model (and therefore not associated with the equivalent ethical issues as type 1), the ERG's original approach to modelling carer disutility has been applied in the base case, and the revised carer disutility modelling approach is applied in a scenario analysis, resulting in an ICER of £[redacted]. In addition, as per the ERG's preference for alignment with TA588, three carers have been assumed for the 'not sitting' state in the type 2/3 model base case. Overall, the carer QoL gains with this new approach are supported by clinicians and a carer expert confirming that QoL would not be lower if a patient was on risdiplam compared to BSC.[10] As indicated by the SUNFISH data outlined above, carer-reported independence as measured by SMAIS increased after 12 months with risdiplam treatment, and this increase was built upon subsequently as demonstrated by the 24-month data.[1] This increase in independence with risdiplam treatment translates to improved QoL for both patients and carers. Additionally, risdiplam patients overall are assumed to be in better health states than BSC patients whilst they are alive, and this functional gain combined with carer QoL loss from bereavement being delayed results in overall improved carer QALYs. Roche acknowledges that the approach may still not represent complete likeness to the real-world scenario, and would like to ask the Committee to consider flexibility in decision making, given the challenges to accurately model the effect of risdiplam treatment on carer QoL.
8	**<u>Bulbar function, respiratory and scoliosis disutilities and costs</u>** During the first Appraisal Committee Meeting, Roche noted that some benefits of risdiplam treatment, such as improvements in respiratory and bulbar function (including swallowing, vocalising and the ability to communicate), were not adequately captured in the models submitted at technical engagement.[3] The Committee was in agreement with Roche that there are likely to be benefits of risdiplam treatment that are not captured in the original models.[3] As such, Roche has updated the models to incorporate additional important aspects of SMA as a disease, in addition to motor milestone achievement, such as scoliosis, requirement for respiratory support and bulbar function. A recent study that subdivided patients into type 1a–c, 2a–b and 3a–b reported that the probability of scoliosis surgery across a patient's lifetime was ~80% in patients with type 1c and 2 SMA, indicating that scoliosis is a common problem affecting the QoL of SMA patients.[14] The requirement for respiratory support in SMA is broadly accepted, with particularly type 1 SMA patients frequently developing respiratory failure prior to 2 years of life.[15] Additionally, a recent study indicated that patients with type 2a SMA experience a rapid decline in respiratory function, needing respiratory support (>16 hours/day) at a mean age of 20 years.[16] Published evidence also confirms that SMA patients frequently encounter bulbar problems, including problems with chewing, swallowing and choking.[17,18] One patient expert that Roche consulted with shared their experience that treatment with risdiplam improved their swallowing function and that this allowed them to eat a wider variety of food with less concern about choking, which impacted both her physical and mental wellbeing.[10] Therefore, disutilities associated with scoliosis, decline in respiratory function and bulbar problems have been applied to the updated type 2/3 and type 1 models, and corresponding costs have additionally been included. Clinical expert opinion confirmed that especially type 1 and weaker type 2 patients are likely to lose bulbar function.[10] Specifically, a clinical expert noted that non-ambulant patients are more likely to experience scoliosis, poor respiratory function and bulbar problems, and that these problems

Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

Consultation on the appraisal consultation document – deadline for comments by 5pm on **Wednesday 23 June 2021.** To be submitted via NICE DOCS.

	are often exacerbated in non-sitters.[10] Therefore, a disutility for each impairment has been introduced in the "not sitting" and "sitting with support" health states in the type 2/3 model base case, and "permanent ventilation" and "not sitting" health states in the type 1 model base case. The following disutilities have been applied: -0.17 for bulbar function (derived from Lloyd et al. [2019][19]), -0.085 for scoliosis (derived from Part 2 of the SUNFISH clinical trial) and -0.07 for respiratory function (derived from Part 2 of the SUNFISH clinical trial). Costs associated with these impairments were sourced from relevant NHS reference costs and applied to the relevant health states; frequencies-per-cycle for the application of each of the impairment-associated costs were informed by a Burden of Illness study conducted by Roche in the UK. Additionally, the proportion of patients experiencing these issues could be expected to be lower in the risdiplam arm in comparison to the BSC arm. As such, an assumption has been made that 100% of BSC patients in these states would experience these impairments, with this value changing to 50% in the risdiplam arm. This is informed by feedback from clinical experts that bulbar function, respiratory ability and scoliosis are all highly interlinked, and they would expect patients to benefit in all three areas upon treatment with risdiplam, across all types of SMA.[10] In addition, the strength of the data seen in these patients to date demonstrates this can be considered an appropriate assumption.
9	The ERG additionally noted that the plateau time point in the models (month 26 for type 2/3 SMA and month 66 for type 1 SMA) had previously been applied one month too early. Roche would like to confirm that this has been rectified in the updated model.

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Consultation on the appraisal consultation document – deadline for comments by 5pm on **Wednesday 23 June 2021.** To be submitted via NICE DOCS.

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Appendix to ID1631 Risdiplam ACD Stakeholder Comments Form

Cost-Effectiveness Results from the Updated Models

Table 1: Revised base case results for the type 2/3 SMA model (PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	20.33	-8.86	-	-	-	-
Risdiplam	[redacted]	22.00	11.86	[redacted]	1.67	20.72	[redacted]

Costs and benefits discounted at 3.5%. BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 2: Scenario analysis results for the type 2/3 SMA model (PAS price)

Scenario	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Base case including company's revised approach to modelling caregiver QALYs	[redacted]	1.67	20.05	[redacted]

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 3: Scenario analysis results for the type 2/3 SMA model (PAS price)

Scenario	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Base case including original Roche caregiver QALY approach	[redacted]	1.67	22.08	[redacted]

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 4: Revised results for the type 1 SMA model (PAS price): Company updated caregiver QALY approach

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	5.81	-5.77	-	-	-	-
Risdiplam	[redacted]	15.95	4.65	[redacted]	10.14	10.43	[redacted]

Costs and benefits discounted at 3.5%. BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 5: Revised results for the type 1 SMA model (PAS price): ERG base-case including caregiver QALY 'cap'

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	5.81	-7.35	-	-	-	-
Risdiplam	[redacted]	15.95	7.29	[redacted]	10.14	14.64	[redacted]

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 6: Revised results for the type 1 SMA model (PAS price): Original Roche caregiver QALY approach

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	5.81	3.58	-	-	-	-
Risdiplam	[redacted]	15.95	33.89	[redacted]	10.14	30.32	[redacted]

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Roche currently have 221 patients enrolled in the risdiplam EAMS programme. Of the 221, 24 are Type 1 and the remaining are Type 2 (the EAMS was not available to Type 3 patients). Based on feedback from NHSE in addition to our EAMS patient numbers, we predict the risdiplam uptake in Type 1 patients to be approximately 10%, whereas the uptake in Type 2/3 patients will be approximately 90%. Based on these

proportions, if we take a weighted average using the highest and lowest Type 1 ICERs and the base-case Type 2/3 ICER, the ICERs are [redacted] and [redacted] respectively.

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Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**SMA UK and MDUK**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Neither organisation has past or current direct or indirect links to , or funding from, the tobacco industry**
Name of commentator person completing form:	[redacted]

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

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Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

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Example 1	We are concerned that this recommendation may imply that ……..
1	**We are disappointed by NICE's initial 'no' to recommending risdiplam for NHS funding.**
2	**Has all of the relevant evidence been taken into account?** NICE's summary indicates that the committee heard, and has taken into account, the evidence put forward by clinical and patient experts. We welcome this. Please see further related responses in comments 3 - 6.
3	**The classification system discussion** '*the committee acknowledged the limitations of the current SMA classification system but concluded that it had been used in the marketing authorisation and clinical evidence for risdiplam'*. **(3.2)** We hope that, for all the reasons stated in our original submission and presented at the 'NICE Review of access for those with SMA Type 3 to nusinersen', this conclusion confirms that if risdiplam is finally recommended, there will not be any barrier to access based on the clinical classification SMA Type 1, 2 or 3 of a child, young person or adult's SMA.
4	**The impact of SMA** *'The committee concluded that SMA has a substantial effect on the quality of life of patients, caregivers and their families'*. **(3.3)** We are pleased that this patient group evidence has been heard and is considered. We note however, that there remains a debate over caregiver QALYs – please see 13. below.
5	**Risdiplam is an Innovative treatment that will meet an unmet need** Patient groups, '*commented that an oral treatment option would be welcome and would also address several issues related to the delivery of nusinersen including the use of sedation, radiographic imaging and anxiety associated with lumbar puncture*.' (3.4) *'supportive treatments do not affect disease progression, so people with SMA will ultimately become dependent on their families and carers'*. (3.4) '*treatment options used routinely in the NHS in England are currently limited and there is an unmet need for people with SMA1' (3.4)* As described in all submissions from patient and clinical experts, a treatment that may be administered at home is a hugely important option. It avoids the costs and logistical challenges to adults and families with children of regular, lifelong travel for treatment. It also eliminates the need for a particularly invasive procedure that is not possible for many with SMA.
6	**The future possibility of switching between treatments** '*The NHS England commissioning expert described the potential treatment pathway if risdiplam were to be recommended as a treatment option alongside nusinersen and onasemnogene abeparvovec. They explained that repeated treatment switching would only be expected in exceptional circumstances, related to issues such as fertility or side effects.'* (3.4)

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Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

Consultation on the appraisal consultation document – deadline for comments by 5pm on **Wednesday 23 June 2021.** To be submitted via NICE DOCS.

	We were pleased to hear this open discussion and that the need for this possibility has been acknowledged. If risdiplam is recommended, we would ask however that the following is taken into account: '*The committee recalled that some people who have had nusinersen may have preferred not to have it, but it was the only option available'* (3.4) The committee also noted that '*the company stated that there is no plausible biological rationale to expect the treatment effect to differ based on prior treatment because both nusinersen and risdiplam have a similar mechanism of action (they are both SMN2 RNA splicing modifiers).'* (3.6) If risdiplam is recommended, we would want all those currently receiving nusinersen to have discussions with their clinical team and the opportunity of switching treatment and, unless there is a clinical safety issue, the possibility of a switch. We hope that the company's assurance as above and the trust we have in our clinical colleagues will mean that the committee's comment that it *'concluded that it had not seen any evidence for people who have had nusinersen and agreed to take this into account when making its recommendations'* (3.6) would not prevent such a recommendation. We hope that the company's comment above that was noted by the committee, will provide sufficient evidence to support switching in any of the circumstances described in this section.
7	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** **Clinical effectiveness** **Clinical trials** The summaries of the clinical trials provide the base case for NICE. We note the SUNFISH age criteria of 2 – 25 years and that the study excluded patients clinically classified as SMA type 3 SMA who were able to walk. We would be concerned if the lack of evidence for this group were to lead the committee to conclude that this group should be excluded for access to treatment. We reiterate this comment from our survey respondent included in our original submission that summarises the progressive nature of this condition: "*The diagnosis needs to be as dynamic as the condition…The etymology of the disease dictates that wherever people start on the continuum of SMA they are on an ever-decreasing scale. As such if you start as a type 3 or type 2 eventually those people have the same end point."* We note that FIREFISH - 41 patients aged 1 month to 7 months with type 1 SMA and two SMN2 copies, excluded patients who had previous treatment and those having chronic ventilation. We are keen for clinicians to comment to NICE as to whether these exclusions would be appropriate in the real world setting and for NICE to hear and respond to this. We are also keen for assurance that these criteria would not be used for others seeking this treatment. We are aware there was no restriction on ventilation support for the risdiplam EAMS and know of two adults, unable to access nusinersen, who would not be able to access treatment if this was a criterion for exclusion. They have both been relieved to be accepted on the EAMS and finally have the opportunity for treatment. Both are supported by

	24 hr ventilatory support, live full work and leisure lives and are seeking stabilisation of their condition. We note that clinical trials have age restrictions to protect the integrity of their data. We are pleased that NICE noted that children are diagnosed with SMA Type 1 later than 7 months and are keen that there is no diagnosis age limit for access for children with SMA Type 1. We note that *'The committee agreed that the clinical evidence showed improved motor function with risdiplam but noted that overall survival data were only available for type 1 SMA'* (3.8) We would not expect to see survival data for SMA Type 2 and 3 given that the natural history life expectancy for the participants would have exceeded the length of the clinical trials. In terms of long-term outcomes, it is ethically challenging to expect a long term 'placebo-controlled period' (3.9) in a rare condition where patients are declining progressively when a treatment has been shown to have efficacy.
8	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** **Clinical effectiveness** **Real world evidence** We are pleased to see that the committee noted, '*The patient experts described their experiences of using risdiplam and noted improvements in motor function, lung capacity, energy levels and stamina. They explained that even very small improvements in fine motor skills and upper limb function were very important because they allow patients to maintain independence. They emphasised that although the studies showed improvements in motor function, they would also highly value a treatment that keeps the disease stable and stops it getting worse'*. (3.8) We cannot emphasise enough the importance of the outcome of achieving stabilisation as highlighted in our submission and evidenced by the 2019 SMA Europe's Community survey In 2019, when **96.7% of 1,327 validated responses** stated they would "*consider it to be progress if there was a drug to stabilize their current clinical state*." We note also, '*The clinical experts explained that there was considerable uncertainty about the long-term benefits of risdiplam but in their clinical experience the results were promising' (3.9).* We also noted a final comment at the committee hearing from one of the clinical experts who stated that their early experience of caring for people enrolled in the risdiplam EAMS was that she was noting an impact on swallowing and respiratory function. This was also raised by the adult patient expert in their evidence following a relatively short time (some months) taking risdiplam.
9	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** **Cost effectiveness** We were encouraged at the committee meeting to hear that the company and ERG, were both willing to discuss the challenges of the economic modelling and report back to NICE. Please see further comments in 10 – 14.
10	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

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Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

Consultation on the appraisal consultation document – deadline for comments by 5pm on **Wednesday 23 June 2021.** To be submitted via NICE DOCS.

	Cost effectiveness **Utility values – fine motor skills** We draw attention to the following comment which is one we hear echoed in the SMA community many times '*The patient experts described the importance of maintaining upper limb function because it allows independence. They explained that some benefits were not captured in the available motor function scales because even small improvements were highly valued by patients and made a large difference to health-related quality of life'*. (3.12) We consider there is a need to adjust the modelling to reflect this in a way that incorporates a '*utility gain to reflect risdiplam's potential benefits in fine motor skills*' (3.12) and that it is, as the committee suggests one that reflects their observation that '*The company's utility gain for fine motor skills is acceptable but may be too low'*. (3.16)
11	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** **Cost effectiveness** **Utility values – other benefits** We agree with this comment: '*The company suggested that the models do not adequately reflect all potential benefits of risdiplam because the benefits of improvements in respiratory and bulbar function (such as swallowing, vocalising and the ability to communicate) may not have been adequately captured in the models'*. (3.17) We note that '*The committee concluded that there could be some benefits that are not captured in the models'* (3.17). We hope to see adjustments to the modelling that reflect this.
12	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** **Cost effectiveness** **Caregiver QALYs** We are concerned that this modelling resulted in, '*The counterintuitive results in the type 1 model meant that a life-extending treatment was considered less cost effective when including caregiver utilities (see section 3.13)*' (3.22) and hope that this will be addressed. We are not health economists but suggest that modelling needs to reflect the differences that SMA UK's experience suggests occur – see our summary below. (Please note this was a table 2 x 2 which is easier to follow but this template does not allow this) **Caregiver Type 1 <u>– infant with no treatment - best supportive care</u>** ➢ **During infant's lifetime – compared to treated infant** **Impact is more intense but for shorter period** • Night and day care 24/7 – very intense and increasing – ongoing chronic care and acute issue • Frequent hospital admissions – disruption to family life / work / siblings • High stress and depression – no hope • Lack of sleep and fatigue • Lack of social contact • Guilt – genetic inheritance • Intense use of equipment at home

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	• Marital stress • Impact on other siblings • Loss of work – invariably one carer at least - financial impact • High impact on extended family – need for their support and of friends and family ➢ **After death– compared to treated infant** **Impact may be similar** • Grief/ Depression / ongoing mental health impact – on carers and siblings • Not infrequent marital / family breakdown • Return to work /social life challenges We note also that as clinical evidence suggests the earlier the treatment, the more positive the outcome, the assumption that treatment leads to care equivalent to Type 2 may be incorrect and caregiver impact may potentially be reduced further than outlined below. **Caregiver Type 1 – <u>infant with treatment</u>** **Based on assumptions that treatment is given early, infant responds well and moves to at least Type 2 / 3 care needs** ➢ **During infant's lifetime - compared to non-treated (best supportive care)** **Impact drops for some aspects but increases for others and new pressures emerge over time** **Decreases:** • Night and day care hours– chronic needs decrease, acute episodes become less frequent • Hospital admissions • Hope decreases stress and depression • Lack of sleep and fatigue - improves • Lack of social contact – may improve • Guilt – genetic inheritance –may be less as able to address this better via treatment **Increases** • Equipment and adaptation needs **Not known:** • Marital stress may continue due to sustaining care • Impact on other siblings may continue due to sustaining care • Loss of work – may continue until FT education is possible - financial impact **After death** **Impact may be similar** • As family has been able to do all possible for their child during their lifetime this may help with feelings of guilt and depression **but** Other impacts of grief and loss remain for all affected
13	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** **Cost effectiveness** **Stopping rules** We note this comment, '*Clinical advice to the company suggested that a time-based rule*

Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

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	may be easy to implement in the NHS in England and may be preferred to the current criteria set out in TA588 because it would avoid pressure for continuous motor milestone improvement. The clinical and patient experts agreed that the current stopping rules in TA588 were problematic and put undue strain on patients and their caregivers'. (3.11) *'the committee concluded that the company's stopping rules may not be appropriate, and it would like to see stopping rules based on clinical criteria that have been agreed with clinical and patient experts'* (3.11) We suggest that these comments were made prior to work following the NICE nusinersen access for those who have SMA Type 3 decision, that led to a revision of these stopping rules. These new measures have been agreed by clinicians and patient groups. They now reflect the desired outcome of stabilisation and greater flexibility in terms of the use of scales and measurements that will reflect this and that recognise the importance of stabilisation of fine motor skills. There is a lay summary here: https://smauk.org.uk/blog/treatments-research/how-scales-and-measurements-will-work-now-for-englands-maa-for-nusinersen We acknowledge the limitations of scales that are insufficiently sensitive to capture subtle changes and that currently the all-important Patient Reported Outcome Measures (PROMS are not collected. We suggest that this information is important for any future decisions and to assist with ascertaining which drugs work better for which groups. We are aware that this does present extra work and time for clinicians, in particular physiotherapists, and can be onerous for families / adults but imagine that they would all welcome the opportunity to add to the pool of knowledge about treatment efficacy. If measurements and stopping rules can operate without NICE / NHSE's involvement but as part of clinical research funded via other routes, we would be in favour of this possibility.
14	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** **Cost effectiveness** **Price** We hope that every effort is being made by the company and NHSE's commercial arm to reach an agreed price that will allow this treatment to be recommended.
15	**Are the recommendations sound and a suitable basis for guidance to the NHS?** Until such time as the economic modelling issues and costs have been addressed, we don't consider the 'no' to NHS funding recommendation to be a sound and a suitable basis for guidance to the NHS. The consultation paper notes *'Risdiplam has features that are commonly seen in treatments assessed by the highly specialised technologies programme, but it was considered as a single technology appraisal.*' (3.21) The committee assures us that '*The decision making takes into account the rarity and severity of the disease'* (3.21) We remain concerned by the constraints of the STA system. We point out that nusinersen treatment was recommended following considerable work on the economic modelling and costs and that this was within the STA framework. We suggest that the clinical and real-world evidence of effectiveness for risdiplam heard by the committee is as robust as possible for any new treatment for a rare condition and note its innovative nature. We remind everyone involved in this appraisal, that for people who live with this progressive

Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

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	condition, every day counts and that their lives could be changed significantly and positively by this treatment. We would therefore expect work on the economic modelling and price to conclude swiftly and positively. We would expect NICE to enable any flexibility the STA process allowed for nusinersen to be enacted for risdiplam, resulting in a positive recommendation.
16	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity** **'***The committee acknowledged that the population eligible for risdiplam has serious disabilities. It acknowledged and considered the nature of the eligible population as part of its decision making'* (3.2) We hope that this decision making included that this is a home delivered option which acts in its favour in terms of enabling equality of access to disabled people. Many face significant challenges having to travel for treatment. During the pandemic many have had to shield and the prospect of travel, hospital visits for care and treatment and exposure to possible infection has been out of the question. Additionally, the option of nusinersen is not clinically safe / possible for many and they currently have no treatment options. We suggest these factors mean that risdiplam should be given special consideration.

Insert extra rows as needed

Checklist for submitting comments

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

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

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

Comment number	**Comments** Insert each comment in a new row.

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Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Has all of the relevant evidence been taken into account? Most of the relevant evidence has been accepted. However, we feel that not all has been reviewed to suitable degree or interpreted to it's full extend. For example, TreatSMA submitted survey results clearly showing that in an untreated population the decline is inevitable (10 years timeframe) and that stabilisation (at least) is achieved in the treated population. However the treatment assessed on how much gain is observed in very short (2-3 years) time span. It is expected that over 10 years period the difference would be more significant, but as this new drug, it cannot be observed just yet.
2	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Whilst we feel a good effort has been put into summaries of clinical and cost effectiveness, the true impact of the treatment on patients health and real life is underestimated. Clinical record of moving fingers does not score points on scales and therefore does not add points to the economic model. On the other hand it allows person to use power wheelchair to move around. Increase in vocal strength has zero points on scales on no impact on the model, but it can get voice activated IT to work better or allows child to participate in school activities more. These little nuances are not taken into account, but they have massive impacts on the life of individual and therefore should affect the cost effectiveness of the treatment. Furthermore, we completely disagree with the model used for the loss of life and impact it has on caregivers and parents. The impact is dramatic and negative and very long lasting. Majority of the families we know have not gotten over this tragedy and continue to suffer mentally and expressing it physically - substance abuse, self harm, eating/drinking disorders, suicide(s) to name few. All of which has long term implications on NHS resources.
3	Are the recommendations sound and a suitable basis for guidance to the NHS? No. We believe this is not the case. We feel that the really sticky point is the costs of the treatment. Therefore, we feel that pharmaceutical company and NHSE must find a financial agreement to resolve the difficulties and thus paving the way for suitable recommendations from NICE.
4	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? No.
5	TreatSMA believes that a negative outcome of this appraisal is not acceptable and leaves significant prevalent population of people with SMA unable to access much needed treatment. We feel that evidence and models used in the assessment do not illustrate the picture to its fullest. The benefits gained by patients are undervalued in commercial model and viewed from basic heath economics without translation of how this gains/stabilisation impacts people in real life. In short we feel that there is more work that needs to go into this and most importantly the costs of the treatment should also be looked at by company.
6	

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
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than 1 set of comments from each organisation.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Adult SMA REACH, Newcastle University and Newcastle upon Tyne Trust**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[]
Name of commentator person completing form:	[redacted]

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Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that people with complex spines likes scoliosis or spinal surgery, who may technically be eligible to Nusinersen, will either not receive any treatment because more challenging or need to undergo a more invasive and higher risk repeat procedures. This group of patients is likely to also have respiratory insufficiency which will contribute to the high risk. We are concerned that this group is discriminated because of their severe disability. An oral treatment is for this group a more suitable option
2	In our clinical practice we observe that fatigue and endurance are also relevant in SMA. these have not been assessed in the clinical trials and data submitted but may and will be available in real world setting but contribute to patients independence
3	An oral treatment may be more suitable for patients who have an active life (higher education, job, family, social) and choose to avoid hospital appointments
4	Data on effectiveness of risdiplam post exposure to Nusinersen should be available in real world data setting because some patients have been switched when the administration of Nusinersen was no longer suitable
5	We have concerns that over the past year patients who were eligible to Nusinersen, were not started on treatment because of the COVID-19 pandemic having affected many wards and departments resulting in only few adult SMA centre starting adults on Nusinersen. The likelihood is that this will continue for some time. An oral treatment would result in patients accessing treatment earlier which would avoid further decline
6	From our clinical experience and data presented, in adult SMA a meaningful change is to be expected over the 24 months of treatment with some benefit which may be observed even sooner but may not necessarily be statistically significant

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Investigators in the SMA REACH UK network Colleagues who have collaborated to this document are [redacted]

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Name of commentator person completing form:	[redacted]

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Example 1	We are concerned that this recommendation may imply that ……..
GB; FM; MS	I am concerned that this recommendation may imply that patients who cannot receive Nusinersen due to previous spinal surgery or severe scoliosis, and/or significant anxiety with lumbar puncture procedures, will be excluded to receive an effective treatment. Risdiplam could be represent a valid and effective alternative in maintaining or even improving motor function and or respiratory function. Patients and clinician involved in the care of SMA patients have discussed this options at multiple meetings of the SMA REACH consortium, with highly convergent views on the desirability to use Risdiplam in patients left with no available medication.
GB	Data from the Firefish study have shown unexpected benefits not only on survival and achievement of motor milestones, but also on preservation of bulbar function. Natural history data show that the majority of untreated SMA 1 children will require tube-feeding or gastrostomy by 10 months of age. Available evidence in SMA 1 patients treated with Nusinersen suggests that unlike motor function, bulbar function and swallowing abilities keep deteriorating despite ongoing treatment, and the majority of Nusinersen-treated SMA 1 patients end up with being tube fed over time. This could be related to the biodistribution of Nusinersen as suggested by recent postmortem data indicating a gradient of AON uptake the highest in the lumbar motor neurons, the lowest in the bulbar motorneurons. The preliminary data from Risdiplam in the Firefish study suggest a high degree of bulbar function efficacy, with consequent benefits in terms of reduced burden to patients and family as well as reduced costs for the health system.
MI ; FM	Regarding the question about long-term efficacy for risdiplam- this was not available for nusinersen (nor for zolgesma) at the time it was evaluated. However data to date indicates comparably favourable outcome measures especially with respect to bulbar function when Risdiplam is compared to nusinersen, with no sign of loss of function at least during the duration of these studies in the population studied. From this perspective, similar consideration obviously apply to the other drugs for SMA. But this is a rare disease with high morbidity and (in SMA1) mortality and increasing SMN level should address the route cause of the disease
MI	*Longterm cost/benefit ratio*

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	The suggested price of £7,900 per 80mg vial appears excessive, also considering that the vials have a limited shelf life. This clearly should be reconsidered. *At the same time the appraisal documents fail to acknowledge the 'costs' surrounding repeated intrathecal injections required for nusinersen including:* *NHS resource use- appropriate infrastructure, clinical space, nursing support, trained treating physician availability, pharmacy time, input from interventional radiology consultants for complex spines, need for specialist nursing/play therapist support.* *Some children are unable to receive treatment without general anaesthetic conferring additional risk in vulnerable children.* *Furthermore there is a significant impact on the patient and carers/family- regular journeys to the neuromuscular centre, taking time off school and work, impacting on quality of life.* *The psycho/socio/economic impact of repeated IT injections needs to be considered based on the evidence currently available for risdiplam as an oral treatment.* *While it is understood that nusinersen is not routinely commissioned as under MAA, we are concerned that these various parametres should be given through consideration by the committee*
MI	*As a clinician with experience over the past 7 years in treating children and their families with SMA, I have had opportunity to follow these families overtime, guiding them through choices and questions about emerging treatments, licensed and otherwise and their suitability/eligibility.* *We have established relationships with Biogen, Roche and Novartis representatives, I engage with SMAUK, we are an SMA REACH site and actively participate in the UK network meetings.* *I feel that patients with SMA1,2 and 3 should be able to access risdiplam with clearly defined starting and stopping criteria, within the terms of a MAA perhaps and utilisation of SMA REACH.* *Starting criteria could include:* *1) Fulfilling stopping criteria for nusinersen,* *2) Repeated intrathecal injections are deemed not in the best interests of the child/family from a psychosocial wellbeing perspective or due to requirement of intense Interventional radiology input or repeated general anaesthetics."*
6	

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Insert organisation name**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Insert disclosure here**]
Name of commentator person completing form:	**Anne-Marie Childs**

Comment number	**Comments** Insert each comment in a new row.

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Example 1	We are concerned that this recommendation may imply that ……..
1	I have some concerns about best supportive care being used as the comparator for Risdiplam treatment The vast majority of children and young people presenting with Spinal Muscular Atrophy (SMA) are now receiving treatment with disease modifying drugs Nusinersen has been available for those with SMA type 1 and 2, and for those with type 3 SMA who remain ambulant since the opening of the Managed Access Agreement (MAA) in July 2019 and prior to that via the Company's Extended Access programme for those with SMA type 1 Those with SMA type 3a who had lost ambulation were originally excluded from treatment under the MAA, but following NICE review of the evidence in April 2021, these patients can now access treatment Effectively only those with complex spinal anatomy or in whom repeated Lumbar puncture (LP) is not safe or feasible are now precluded from treatment. Initiating Nusinersen treatment in the adult population has been a more protracted process and there are adults managed by NM services that have not been able to deliver the treatment for practical reasons Since the opening of the EAMS in 2020, many of these individuals are now receiving Risdiplam Onasemnogene treatment for infants < 13m with type 1 SMA is now being delivered in the 4 infusion sites selected by NHSE. Older infants and children with SMA type 1 < 21kg in weight are also able to access treatment via the NHSE agreement with Novartis. Therefore in practice the majority of children and young people are receiving disease modifying drugs and not best supportive care. In my service, I manage 41 children < 19 yrs with SMA. 27 are receiving Nusinersen, 10 are receiving Risdiplam via the EAMS, and 2 are presymptomatic, with 1 awaiting treatment with onasemnogene next week and only 1/41 children (an ambulant SMA type 3 patient) receiving best supportive care. This is likely to be the case for the majority of children's SMA centres across the UK Thus clinical experience from a large centre confirms that there is an unmet need for an SMN2 modifying drug that can be delivered orally (25% of our children's cohort) but also that very few children and young people are simply receiving best supportive care
2	I also agree with the committee's view that the company's model overestimates the life expectancy of those whose SMA type 1 is managed with best supportive care, as the figures generated do not reflect clinical experience. I believe it would be more accurate to model the survival in the untreated group on data from natural history studies (Finkel et al) and indeed the control arm of the Endear study
3	I agree that there is no peer reviewed data to determine the long term effect of Risdiplam and that it would be appropriate to include some form of 'stopping' criteria for its use, along the lines of the MAA for Nusinersen. It would not be appropriate to continue to prescribe the drug if there was no evidence to support its effectiveness. The committee have agreed with patient and clinical experts that stabilisation of functional abilities is a positive outcome in a progressive condition like SMA. In my experience, it is possible to apply a combination of standardised functional assessments in a systematic and objective way to identify those whose condition has failed to respond to treatment. However, it is important to 'select' the appropriate tools to capture the full range of benefits of treatment. Crude assessment of motor milestones will fail to pick up more subtle benefits in fine motor skills and upper limb function that are of significant value to individuals and their ability to participate in society, maintain their independence and lead good quality lives. However, given the challenges and complexities of applying such assessments, it may be possible

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	that a combination of 'time' with the most appropriate functional and QofL assessments could be used The clinical benefits seen in the respiratory and bulbar function of a systemically delivered treatment like Risdiplam have not been adequately captured in the models, although the trend in improvements can be seen when comparing the outcomes at 1 year of treatment with Nusinersen (Endear) and Risdiplam (Firefish).The benefits will not only impact individual patients but also their care givers and hospital services. Respiratory impairment results in recurrent infections and hypoventilation and is the most likely cause of unplanned and protracted hospital admissions in SMA, including admission to critical care units. It is the main factor underlying the reduced life expectancy seen in SMA types 1 and 2
4	I agree that the Health utility values used to identify the gains in upper limb function underestimate the beneficial effects of treatment. Maintaining the capacity to independently transfer, dress and feed oneself are hugely significant. Preserving or improving fine motor skills can mean the difference between participation in education/workplace activites as well as being able to operate controls for powered chairs/equipment and the environment. Such 'control' is vital to emotional and psychological well being and should equate to a higher HU score The reduced burden for caregivers, outlined powerfully by patient experts should also be captured in the model. The costs benefits of reduced 'face to face' care needs and potential for active participation in the workplace should also be considered
5	I have concerns about a model that assumes that premature death of an infant with SMA 1 is somehow beneficial to caregivers and feel this is an unacceptable position. In my experience this is not the case, infants with SMA type 1 have good cognition and even very weak infants enjoy positive interactions with their family and loved ones. Recurrent hospital admissions to support feeding and breathing difficulties have a considerable impact on the child and family's quality of life and the extent and severity of respiratory impairment is the most important factor determining life expectancy. Failing to model the benefits of Risdiplam on bulbar and respiratory function, and simply focusing on gross motor milestones will underestimate the cost benefits of therapy
6	Without Risdplam, a considerable number of SMA patients will be left without access to any disease modifying drugs, particularly those with late onset type 2/3 SMA with complex spinal anatomy and those who cannot tolerate repeated lumbar puncture. Untreated, these patients will decline in their functional abilities, becoming more dependent on carers and clinical services particularly when the inevitable changes in respiratory and bulbar function occur (Trucco et al) By failing to consider the comparative costs of other licensed disease modifying drugs, and their delivery, and by using models that fail to capture the wider functional benefits of treatment, we risk failing to deliver effective therapeutic treatment to a large subgroup of SMA patients increasing the burden of disease to the individual, their carers and health care providers.

Insert extra rows as needed

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Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	N/A
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

I have expressed many of our thoughts in the close questions. However, the other significant situation as parents is that we have always been open with our son about his SMA2 and why we do things but recognise (as with so many children with SMA) that he is a bright boy, who as he gets older, should be involved in the decision making process (just as he is about who his carers are and how they might help him etc). It did not sit comfortably with us to force him to take nusinersen just because we fulfilled the criteria, especially when we weren't sure how significant an impact it would make. The relationship we have with our son is paramount as we, as a family, will continue to have to face many things together and we negotiate life living with a disability. For any treatment to be a success, we know that we need him to be 'on board' as he is well aware that this is his body which he can make choices over. As I said, children with SMA often have a heightened emotional and social development, and are very 'switched on'. He was not 'on board' with nusinersen, and whilst we have kept the conversation open, it has been hard to promote such an invasive, medicalised and potentially risky procedure despite all its potential benefits. Knowing that risdiplam is a future possibility gives him hope. Our sadness is that we were not allowed to be part of the Early Access Programme even with his strong aversion to needles, and the spinal procedure, because technically and clinically he met the criteria for nusinersen. It has put us in an impossible position where we could risk our relationship with him if we forced this decision which could then have an impact on his mental and physical well being, his education, his right to an opinion which he should be able to express and should be listened to and heard. This may not be measurable evidence but it is a real experience. So we are now in the situation, where our ideal approach of risdiplam which suits our son, and our family hangs in the balance whilst we have to re-visit again the anxiety of looking at nusinersen which may end up having a more negative impact on our lifestyle as more time in school will be lost. Our son is also being made to be even more aware of his 'disability' as an issue when our approach has always to be to get on with things so that he can be like everyone else. He doesn't like the attention of being 'different' not because of his powerchair but because he often has to miss what his friends are doing at school because of appointments! It is hard enough as it is to live in a mainstream world, but our son is a happy, positive balanced boy and we want to maintain that. He dreams big. He lives with a severe disability but doesn't see that should mean he is treated differently. He is prepared to go out there and live and does not want his personality to be defined as his disability. A medication like risdiplam would enable him to keep that attitude whilst doing something proactive to help his condition. He just wants to do the fun things in life. Having risdiplam would also release the neurology teams to focus on those who do need very

specific treatments, whilst allowing the rest of us to 'get on with it' with the best possible outcomes. To me that is cost effective. The recent advances for the treatment of SMA are incredible and truly life changing. Those who have SMA are incredible people with tremendous and equal value to everyone else. Having rispdipalm available, will enable those with SMA to live an even more full life and give back to society 100 fold. The approval of NICE would recognise this value.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

In my opinion, no, as there is more to measuring the worth of something than money alone. This is such an incredible breakthrough that it is worth supporting.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

I am re-emphasising these points as many I do believe would have positive impact on the NHS and the individuals involved. The oral treatment of Risdiplam would be of huge significance for a family like ours. We have always just got on with making our life as good as it could possibly be for our son. When nusinersen arrived, it took us by surprise a bit as it suddenly seemed to medicalise our son's condition in a way we hadn't expected, as after we had been for the assessment, we were talking about a very invasive process of lumbar punctures, general anaesthetic and an uncertainty as to what degree this may help. Once our son realised it wouldn't enable him to walk, he completely rejected the whole procedure. He said if he could take something, that would be better as yes he would like to be stronger, but on balance he said he was 'happy in his skin' and didn't want all the needles. We were then faced with a difficult situation as parents as we didn't feel comfortable with 'forcing' an eight year old to go through a very invasive procedure. We felt he would have to be on board, and whilst we have revisited the options, his response was always the same. At this time we began to find out about Risdiplam which seems to offer a family like ours so much more. It could be given at home which would maintain 'normality' of life; it avoided the anxiety of the child and all of the family ahead of each injection whilst seeming to give the same benefits; it appeared to be working well in patients in other countries; it allowed the children to maintain a quality of life that avoided even more hospital visits and professionals in their lives; allowed education to continue undisrupted (an underestimated but highly important benefit); avoided long journeys to the hospital (we are 1.5 hours from the hospital); avoided time being taken off work and additional childcare being sought for other family members; seemed to be a cost effective alternative to injections which are also dependent on a team being constantly in place; removed the anxiety of travel during the ongoing covid pandemic. There are just so many benefits. In addition, having risdiplam would give the patients a choice as to what the best route for them was. To have that choice is of immense value.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

The patient voice and a right to choice needs to be heard more. Those making the decisions should listen to the impact on those who give care and live with the every day reality of caring for someone with SMA.

- Section 1.1

This is a drug that can be taken at home without impacting on daily life to the extent of nusinersen does (with visits to hospital, blood tests, clinicians, consultants, travelling, anxiety, unpredictability - local anaesthetic vs General anaesthetic, impact of scoliosis, time lost in education).

- Section 1.2

It is unfair that those who may be clinically viable for nusinersen have not been able to make a decision to be on the early access programme for risdiplam if they have a severe aversion to having a spinal injection. It is very short sighted to not have taken into account the mental anxiety and stress that this may cause both to the children and parents.

- Section 2.1

All people with SMA should have the opportunity to explore the possibilities with Risdiplam, as it it not a condition that fits neatly into boxes; SMA manifests itself differently in every person who has it despite the similarities in the condition.

- Section 2.3

A decision like this should not be based on price. All costs can change, and with a larger audience wanting to receive Risdiplam, then a more effective price should be negotiated. Medicines like this will pave the way for so much more research which will have an impact on many neuromuscular conditions.

- Section 3.12

It is hard to explain why even minor improvements might have such an impact on a person. It could even be the difference of being able to press a button to access something independently, or hold a pencil to write for longer than 5 minutes, or hold up an ice cream! These are all every day activities which someone without SMA takes for granted but are of immense value to someone with SMA. It maintains the dignity of a person if they can do some of the small actions. It also means that things like friendships and relationships can happen without constant care and supervision being given. When trying to give an example of the degree to which strength is impacted, I have often used a children's storybook with the buttons to press to make the noise in a book. Our son struggles with that as a 9 year old, with a book designed for a 1 year old.

- Section 3.13.

If a carer has a more stable condition to work with, then that would enhance the quality of life for patient and care givers. Our challenge is that this is under constant review with all professionals which is time consuming, disruptive and emotionally draining. With more stability, a more pro-active approach to life can be taken and embedded into every day life. As parents,we know that the situation with our son could change at any moment with the 'wrong' type of cough affecting him and him not having sufficient physical strength to fight it.

- Section 3.1

I agree with this clinical description. In addition to this, it should be noted that SMA presents itself very much as a physical condition and those who have it often have a heightened mental capability, with a very strong awareness of the world, a social awareness of how people behave as they work so closely on an intimate level with so many professionals, and a real desire to go out there and live the lives they have been born to live without barriers. It can be a life limiting condition but with our son we do everything possible to mitigate the effects of his disability through attitude and technology/equipment so that he is empowered to contribute to society. The daily physical challenge is immense as are the barriers that have to be overcome but the aim is very much to live the best life possible.

- Section 3.2

Yes the boundaries between different types of SMA are blurred, and within each type there is huge range of impact. For example with SMA2 which is what I am most familiar with, some may struggle more with swallowing and eating, others with scoliosis, others with respiratory infections and coughing, reduced upper body strength, weight loss or weight gain, being hyperflexive. SMA 1 is very different to SMA2 or 3 but the need to make a difference is very real.

- Section 3.2

When you receive a diagnosis of SMA the immediate impact is of deep, deep shock and sadness, a very real and tangible bereavement as you have to face up to the life that you had dreamed of becoming very different. And then you have to hold your head up and make a decision about the sort of life you wold like to carve out for your child and the approach that you will take. As parents we decided, to live life to the full and create an environment that would allow our son to thrive, to fulfil his potential and to be fully included in society and to enable him to fully contribute to society too. He was to have no barriers to living, and at that point in 2013, there was no medical hope on the horizon, just management strategies. We had to move house which is now fully adapted so that he could have at least one place where everything was accessible and set up for his needs (bathing, hoist, lift, pathways, space for equipment, space for carers) to take some of the everyday pressure away. We have maintained daily physio to give him the best physical chances possible and funded equipment to allow him to access life. When he becomes poorly with chest infections which can develop rapidly, we are on high alert and use early interventions (cough assist, bipap, nebuliser, antibiotics) to minimise the impacts. However, SMA causes fatigue and he can soon become too tired to even cough and breathing becomes a struggle requiring immediate open access to the hospital. When he gets a cold, the lack of strength becomes frightening. However, we have learnt how to keep the 'medical' impacts to a minimum and as a result he is able to live a 'normal' and fully integrated, good quality life. He is 'happy in his skin'. He attends a mainstream primary school and is doing well. However, the daily routine is hard. He requires 24/7 support for all his physical needs: toileting, dressing, brushing his hair, turning in bed, positioning, cutting food, accessing toys, reaching for things, coughing, lifting up when he falls forward, harnessing when getting into the car....All of this takes additional time and is very physical. It is hard for him to rely on others to the extent he does, so the chance to do anything independently is seized upon: it is important and not to be underestimated. It is painful to watch and realise that your child has lost some of the strength they once had when even lifting a cup of water to their mouth is a big movement, and a tiring one. The financial impact is real, and so is the emotional

impact. The whole family is affected, and the whole family is enhanced despite the challenges. Our son asks real questions about what life may be like in the future, he likes to show his 'strength' but as parents we worry about what the future holds for our normal boy who happens to have physical disability. We have to be positive about the future and keep hope.

- Section 3.4

The oral treatment of Risdiplam would be of huge significance for a family like ours. We have always just got on with making our life as good as it could possibly be for our son. When nusinersen arrived, it took us by surprise a bit as it suddenly seemed to medicalise our son's condition in a way we hadn't expected, as after we had been for the assessment, we were talking about a very invasive process of lumbar punctures, general anaesthetic and an uncertainty as to what degree this may help. Once our son realised it wouldn't enable him to walk, he completely rejected the whole procedure. He said if he could take something, that would be better as yes he would like to be stronger, but on balance he said he was 'happy in his skin' and didn't want all the needles. We were then faced with a difficult situation as parents as we didn't feel comfortable with 'forcing' an eight year old to go through a very invasive procedure. We felt he would have to be on board, and whilst we have revisited the options, his response was always the same. At this time we began to find out about Risdiplam which seems to offer a family like ours so much more. It could be given at home which would maintain 'normality' of life; it avoided the anxiety of the child and all of the family ahead of each injection whilst seeming to give the same benefits; it appeared to be working well in patients in other countries; it allowed the children to maintain a quality of life that avoided even more hospital visits and professionals in their lives; allowed education to continue undisrupted (an underestimated but highly important benefit); avoided long journeys to the hospital (we are 1.5 hours from the hospital); avoided time being taken off work and additional childcare being sought for other family members; seemed to be a cost effective alternative to injections which are also dependent on a team being constantly in place; removed the anxiety of travel during the ongoing covid pandemic. There are just so many benefits. In addition, having risdiplam would give the patients a choice as to what the best route for them was. To have that choice is of immense value.

- Section 3.8

Absolutely. Any small changes or improvements in function are of immense consequence to someone with SMA and those who care for them. This cannot be underestimated. Our son is hopeful to maintain what he has with the hope of some small improvements. To him, strength is everything, and will enable him to be as independent as possible. It could be the difference to holding a recorder or not; lifting a fork to his own mouth; pulling a door handle open; choosing a book from the shelf. It could help him to cough up mucus more readily instead of it getting stuck on his lungs and causing infection. He could have more energy to do physical activity like hydrotherapy to help him keep fit, burn off some calories and maintain mental well being. With a more stable condition, he can plan things. If you don't know how you'll be in a year's time, that becomes much harder.

- Section 3.11

I find these decisions over number of years very difficult to understand. It suddenly feels like a judgement about how many years any one person is entitled to. Every

person should have the opportunity to life, and being able to live it to the full. If that is not the case, then those who make those decisions need to look into the eyes of the people who would like this treatment and explain to them why the length of their potential life justifies the outcome of the decision.

- Section 3.18

When we received our diagnosis, there was nothing to give any hope, even though we asked those questions. It all seemed very far away as SMA was so rare. Now we are in this position where we could have a choice of treatment, with one being able to be given in our home. That, to me is innovative, and a real achievement; a game changer for us and how we choose to live our life.

- Section 3.21

The decision making process should recognise that early intervention is key with SMA and could have significant impacts on families. Those being diagnosed now will have a choice which should allow their children to have more options as they grow up. Those who have waited for so long, should have the opportunity to see how the medications available could have an impact.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	N/A
Location	Not specified
Conflict	No
Notes	
Comments on the ACD:	

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I am not sure that you can put a value on the ability to swallow, the ability to breathe unaided.It is multifaceted. If you can swallow,you can eat without need of a feeding tube.You can swallow without risk of aspirating and requiring medication for chest infections etc.You can leave the house and spend time socialising (eating is a social habit) leading to better mental health etc. I am not sure how you assess the cost effectiveness of a medication that can help you keep swallowing.I ask you personally. How much would you pay to be able to swallow food all your life?How much is that worth go you?

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

I think in an economic and political climate that has been keen to give access to health care to all. (That is a national lockdown to prevent the NHS being overwhelmed and therefore ALL,irrespective of age,disability and underlying medical conditions that require treatment for Covid, be given it),it seems discriminatory to on the other hand deny a treatment to a group of individuals where a benefit in research has been shown.For some, with SMA there are no

treatments at all.Risdiplam fills this gap until market alternatives can be found. I am sure that if the threat of SMA was as prevalent in society as Covid 19, a treatment would have been found more quickly and been licenced more quickly.Because a small population is involved, their plight is unheard and their need is unmet.I believe this is discriminatory in itself.To let this small population deteriorate further (as has happened because of delays in licencing nusinersen) really will mean death to some and permanent (and unecessary) long term severe disability to others.

The problem with waiting for long term evidence is that by the time the evidence comes in from the rest of the real world studies a lot of time has been lost for those deteriorating with SMA.The function they loose over time can never be regained,therefore there should be a managed access programme to review the medication while this data is collected.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	N/A
Location	Not specified
Conflict	No
Notes	
Comments on the ACD:	

- Has all of the relevant evidence been taken into account?

Serious consideration to young people who are out of scope of Zolgensma, Nusiurnesen but are on the boundaries of loosing significant independence that have their whole life still to live, that having access to Risdiplam is their only current hope.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

I would like my specific perspective taken into account and reviewed:

After being diagnosed at 18 months old with SMA Type 3, I could walk until 10 and have been completely non-ambulant since the age of 14. I am now 27, I run my own business, compete for GB Paralympic air rifle talent and development squad and have my whole life to live an aspire for. I now find myself in a position due to my spinal fusion at 14 being out of scope for nuisurnersen and potentially never be able to access risdiplam if not approved. To be so young with my whole life to live and still have very basic independence to eat, drink, work and take part in sport, I would love to be able to maintain the limited mobility I have now. The thought of there being two drugs that I cannot access is really starting to effect my mental health, something I have always been in control in. Risdiplam is my only hope to maintain what I have before literally all my independence could be taken away. COVID-19 has caused me to loose a sever amount of muscle mass, whereby I am now struggle to eat my dinner independently, time is critical for me now, I am

running out of time before its to late where I am close to losing a lot of my independence.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	N/A
Location	Not specified
Conflict	No
Notes	
Comments on the ACD:	

To whom it may concern,

I hope this finds you well.

My name is [redacted]. I am a Tax Manager working for a 'big four' financial firm. I am a [redacted]. I am an honours graduate from the University of St Andrews. I have been [redacted].

Today, I am not writing to you in any of these capacities. I am writing to you simply as somebody who suffers from Spinal Muscular Atrophy (SMA) Type 2.

To my regret, I have never been particularly active in the SMA community. For most of my life, SMA was something I lived with quietly in the background, and although it has always dominated many aspects of my life, I preferred not to think about it too much. However, in late November 2020, the wonderful doctors in the muscle team in Newcastle told me that I was eligible to begin a new treatment program, receiving a daily dose of Risdiplam under the early access to medicine scheme. Suddenly, I was thinking about my condition a lot more, but where there had once been concern and anxiety, there was now a growing optimism. On the 18th of December, a week before Christmas, my family and I received the best festive present of our lives when I took my first dose of the drug.

The most truly remarkable aspect of all of this was that this medication was simply 6.6ml of oral liquid. No injections into the spine, no anaesthetic, no surgical element. In fact, no real impact on everyday life. Incredibly easy to take and, for me at least, no side-effects.

For the first 25 and a half years of my life, I was receiving no direct medical treatment for the SMA that was slowly eating away at me, causing my muscles to deteriorate over time. It is difficult to describe the feeling of liberation and hope that I felt on taking the first dose of Risdiplam. It is the memory of that feeling that compelled me to write to you today.

Along with many others, I am disappointed with the recent news that NICE is not recommending Risdiplam for treatment of SMA in the UK at this time. I wanted to take this opportunity to share with you some of the details of my journey with SMA so far, along with some of my thoughts following the publication (2nd of June 2021) of the NICE draft guidance on Risdiplam.

As with most young boys of my generation, growing up at the very beginning of the 21st-century in North East England, many of my earliest memories take place on playing fields. Although my sporting heroes were often the same, unlike my friends I was never able to recreate a David Beckham free-kick, or attempt a ferocious Alan Shearer penalty. Rather than smash balls for six like Kevin Pietersen, I was always the umpire. I was fortunate enough to grow up with some brilliant people around me. I never felt left out, and my friends and family did all that they could to involve me as much as possible. But there is no escaping the fact that it breaks a young boy's heart to be told he will never kick a ball or hold a cricket bat. This was my first experience of the cruel nature of SMA.

Over time, faced with a growing list of things you can't do, it is human nature to start seeking out and focusing on those things you can do. For me, looking back now I guess I decided at an early age that if I wasn't going to be the best at football or cricket, I would make sure I was competing to be the best in the classroom. My early passions for maths and history have stayed with me into adulthood. I studied a maths degree at the University of St Andrews. Moving away to university is an important moment in the life of any young person, and naturally along with that can come a great deal of stress and apprehension. For me this was hugely exacerbated by my condition. Not only was it necessary to contemplate the usual anxieties around moving away from the family home for the first time, but I was also preoccupied with concerns about wheelchair access and the thought of having my care provided entirely by strangers.

I fully recognise that I am not unique in these positions that I describe. In fact, I am all too aware that there are many individuals who are in a far worse position than me, including those people who sadly suffer from the more severe form of SMA and who tragically see their lives cut short in so many cases. This underscores the dual nature of the underlying cruelty of SMA; at its most severe, it can rob innocent, infant sufferers of their lives, while those who live on with the less severe forms are instead forced to watch their bodies weaken over time while their minds continue unaffected. It is not a question of which of these groups have it "better" or "worse". All I can say from my own experience is that it has been helpful to focus on the many special times that I have been lucky enough to enjoy, and the promise of great days to come. There is no better example of the power of Risdiplam than in this simple idea: for the first time in my life, I can now look ahead to the future with a reasonable level of hope that SMA should not take much more from me than it already has. This optimism is not merely blind hope driven only by what I would like to see play out, but instead is based on science and the wonders of modern medicine.

With reference to the draft guidance published by NICE, I note that the general consensus appears to be that the committee recognises the clinical benefit of Risdiplam as a treatment for SMA. Indeed, as the guidance states: "the committee agreed that the clinical trials demonstrate that risdiplam meaningfully improves motor function for people with type 1, 2 and 3 SMA." Anecdotally, I can support this conclusion from my own experiences. Around four weeks after taking my first dose of the medication, I noticed substantial improvement in terms of my ability to support my neck while hoisting and to lift my head from the pillow more independently than before. Simultaneously I also noticed improved grip strength in both hands, meaning everyday tasks such as moving a drink to my mouth was suddenly significantly easier. These are the sort of small gains that can be truly transformational in terms of improving the independence of somebody with SMA. My own personal ambition is that hopefully I will also begin to see some additional improvements to my stamina levels as my treatment with Risdiplam progresses.

Of course, I fully appreciate that decisions around public health are complicated in their nature. There will be a number of factors to be considered from a range of different areas, so I understand that, along with the clinical benefits that already seem to be fully appreciated by NICE, there are also additional matters for consideration in relation to pricing, health economics, administration and logistics, and the relative merits of other treatments. I am not able to comment on these matters directly. The only contribution I can realistically make at this stage is to reiterate what I have already said: there is a human element to all of this, and although it is difficult to quantify objectively, the sense of hope that Risdiplam has given me truly exists and has enormous value. I hope that this is something you consider as the appeal stage progresses.

To conclude, I would like to offer my services in any way that they could be put to use. I would be delighted to engage in any further discussions with any of the relevant parties on this matter - to add the real human voice of a real human being who is currently fortunate enough to be accessing this incredible medicine.

Many thanks for taking the time to read this. I look forward to hearing from you.

Kind regards,
[redacted]

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	N/A
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

There is no indication within the ACD that the patient and carer testimonials delivered at the committee meeting have been considered in the decision-making process. These testimonials have been described as “noted” but it is not clear whether they have had any weighting applied to them. Please clarify the extent to which this relevant evidence has been incorporated into the decision-making process.
Risdiplam is vital to the SMA population as an alternative to nusinersen. As an oral medication it will be suitable in many cases where a lumbar puncture is simply not an option for the patient. The ACD makes many mentions of there being an unmet clinical need, yet there is little, if any, evidence that the appraisal process really seeks to address that unmet clinical need. My son is 24 years old and has type 3 SMA. We have watched him deteriorate to the stage of being unable to walk and being now wheelchair reliant. Without intervention he will only deteriorate further and lose strength in his upper body and respiratory system. The committee heard a powerful testimony from Andi Thornton who is terrified of losing the one link to independence he now has; the ability to use a computer mouse. I challenge the committee to spend a single day of their lives wheelchair bound with the only movement available to them being the ability to use a computer mouse. This is a

future that awaits my son and those with SMA in the absence of their being able to access medication. 24 hours a day, 7 days a week, 52 weeks a year.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The ACD is not clear on the price used in the appraisal process. The list price of the drug is the only price stated yet we are aware Roche are prepared to come to a commercial agreement with the NHS. Therefore, if the list price has been used to complete the appraisal, this will produce an artificially adverse cost effectiveness ratio. Please clarify that the price used in the appraisal represents the actual likely cost to the NHS of the medication.
From personal experience and from that of friends in the SMA community I can say categorically that the day-to-day stress of living with or caring for an individual with SMA is magnified many times when there is an approved and proven effective treatment that is not being made available to the SMA patient for whatsoever reason. Not only do we have to live with the myriad of "business as usual" challenges, but then there is added stress of the constant battle with the NHS to access medication they should already be providing to us. And, in this case, having to read and attempt to understand long and complex documents so we can feedback on the appraisal process (and that is feedback which we have no real confidence will be taken seriously). There is no evidence in the ACD that any multiplication factor has been applied in the appraisal to the stress levels of the patient and carers to reflect this. Therefore, the stress factor used in the appraisal calculations is understated.
Much mention is made in the ACD of "best supportive care" being the best comparator. Clause 3.4 of the ACD refers to "best supportive care" as being intended to "improve quality of life" involving a multi-disciplinary approach including (amongst others) nutritional support, physiotherapy and occupational therapy. This clause further goes on to state "It is recalled that best supportive care is routinely used in clinical practice in the NHS in England". If this is what the committee is being led to believe then the committee is being badly advised. By way of example, in our experience (and we are most definitely not alone in our experiences):

1) My son has not had access to an NHS physiotherapy session for over 6 years now. They are simply not available for the adult SMA population. We do daily stretching exercises with him at home; the only professional physiotherapy sessions he has had since turning 18 are those we have paid for privately and those he has been lucky enough to secure through Muscular Dystrophy UK. The NHS neuromuscular centre looking after my son has one part-time physiotherapist to look after over 9,000 patients;

2) My son was diagnosed with SMA in 2004. In the 17 years since then we have not had any form of contact from a dietician or indeed any professional qualified to provide nutritional advice. The subject has never even been mentioned to us;

3) In February 2020 we attempted to secure an occupational therapist's assessment of Chris's bedroom and wetroom as we were concerned that the set-up was not safe for him and didn't know what we could do to make necessary improvements. We were told to expect to hear something within 15 weeks (a long time to wait in any event but particularly when you've been clear you're concerned for an individual's personal safety). After having to chase we finally got to see an occupational therapist at the end of October 2020 (in excess of an eight month wait).

The above details just 3 examples of how my son is far from receiving “best supportive care”. Does the appraisal process take into account that many, if not all, SMA patients are not receiving anything remotely like “best supportive care”? “Best supportive care” is a pipedream and cannot be assumed in the appraisal process. Please confirm that the appraisal process calculations use a “real-life” approach to what is actually available to SMA patients in terms of “supportive care”.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

The lack of any long-term evidence of Risdiplam’s efficacy should not be used as a determining factor in the decision-making process as there is an unmet clinical need. There is likely to be a lack of long-term evidence with any newly approved drug therefore this is not a credible or fair reason for declining provision of medication where there is an unmet clinical need. The ACD confirms clinical experts having described improvements seen in trials as “promising” and “clinically important”. Further, 3.6 of the ACD refers to nusinersen and states “there is no plausible biological rationale to expect the treatment effect to differ based on prior treatment because both nusinersen and risdiplam have a similar mechanism of action”. Why then does the appraisal process not consider results seen in patients being treated with nusinersen to gain a better indication of the longer-term efficacy of risdiplam?

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

The nature of SMA means that appraisals for any new drug do not sit under NICE’s standard appraisal route or their highly specialised technology route. The fact the ACD mentions that risdiplam would not meet NICE’s criteria for cost-effectiveness even at zero cost to the NHS is a clear illustration of this. Therefore, patients are being discriminated against due the nature of the condition not slotting nicely into one of NICE’s 2 appraisal routes.

SMA sufferers have been badly let down by NICE’s flawed appraisal process in the past (nusinersen) and they continue to be so. With nusinersen, NICE falsely represented that the drug would be “available for all” and subsequently backtracked on this statement. Additionally, NICE did not deliver their decision within documented, or indeed reasonable, timeframes. Nusinersen was approved by the European Medicines Agency on 1 June 2017. On 3 July 2019 (OVER TWO YEARS LATER) the managed access agreement was published (and it is worth noting at this point that most eligible adult patients still can’t access nusinersen due to inefficiencies in the NHS). Four years after the medication was approved, SMA patients (who are deteriorating physically every single day – SMA doesn’t wait for bureaucracy to take its course) are still waiting. With risdiplam, NICE has the opportunity to partly atone for the appalling manner in which SMA patients were treated under the nusinersen appraisal. Yet NICE’s initial stance is to decline SMA patients access to this innovative and much-needed medication! You will therefore understand why the committee’s negative decision will be regarded by all those affected by SMA as particularly cruel.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	N/A
Location	Not specified
Conflict	No
Notes	
Comments on the ACD:	

- Has all of the relevant evidence been taken into account?

No because because Evrysdi does the same job as Spinraza and if Spinraza is available then I think Evrysdi should also be available. Evrysdi is available in lot of other countries and people who are using it finding it effective. I hope NICE will show bit more compassion and allow this drug because SMA is a devastating condition and for people with SMA every day is a hell. I am talking from personal experience because I suffer from SMA Type 3 and every night when I go to sleep I wish I never wake up again.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No because it is cheaper than Spinraza and can be administered at home. No need for the hospital visits or the need for the specialist to administer the drug so there will be savings there.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

I feel NICE should consider from the perspective of SMA patients and try help out whatever way possible.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Since Spinraza is not suitable for everyone because some people had their spines fused or for other reasons, I feel those people will feel being discriminated against because how come some people with the same condition can receive the treatment and others can't. Totally unfair. Based on the facts that Evrysdi is suitable for vast majority of SMA patients, is cheaper than Spinraza, does the same job as Spinraza and can be administered at home, I feel this drug should definitely be available. Also, it will be even more effective when Scholar Rock comes out, which should also be made available. I feel for some of us with SMA, Evrysdi is the only hope so please don't deny us this treatment. I hope committee members and people who have the power to make decisions will show utmost compassion when making their final decision and will also put themselves in our shoes and feel what it's like to live with this debilitating condition and have to depend on others day and night.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	N/A
Location	Not specified
Conflict	No
Notes	
Comments on the ACD:	

- Has all of the relevant evidence been taken into account?

No: The committee acknowledges that the present classification of SMA is not a suitable one for appraising treatment.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No: The clinical effectiveness of the drug does not give enough weight to its ability to halt the progress of the condition. Nor its ability to subtly improve breathing and fine motor skills.
The cost effectiveness of the drug is greater than stated. For example a carer who sacrifices a nursing career at degree level is a cost to society as a whole and a cost to the family.
A carer who becomes unwell becomes an additional burden on the state.
SMA patients can be net contributors to the state who may gradually lose the ability to contribute.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No.

- Section 2.3: “The list price is £7,900 per 60mg/80ml vial. The company has a commercial arrangement, which would have applied if the technology had been recommended.”

It is difficult to comment on an unspecified 'commercial arrangement'

- Section 3.12: “It concluded that the company's utility gain for fine motor skills is acceptable but there is uncertainty around the exact value and the benefit could be larger.”

Agreed.

- Section 3.2: “The committee acknowledged the limitations of the current SMA classification system but concluded that it had been used in the marketing authorisation and clinical evidence for risdiplam.”

If the committee is to pursue clinical excellence should it not advise on a better classification?

- Section 3.3: “The committee concluded that SMA has a substantial effect on the quality of life of patients, caregivers and their families.”

Has this been taken into account when determining the value of a QALY?

- Section 3.11: “In the absence of updated criteria from TA588, the committee concluded that the company's stopping rules may not be appropriate and it would like to see stopping rules based on clinical criteria that have been agreed with clinical and patient experts.”

Agreed.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	N/A
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

It is unlikely that a member of the general public is qualified to answer this question. I am answering the questions a keen follower of progress in treatment of SMA for nearly 18years. Our family know the true physical, emotional and health and financial costs of living and caring for a family member with SMA. Every family's experience is unique and therefore relevant evidence is broad and comparisons difficult to draw. The most relevant evidence to me is that this treatment can be given orally, crosses the blood brain barrier and also is present in the general circulatory system. At the very least it can halt the progressing of SMA and in some cases improve motor function. It also seems that it is more effective at preventing the deterioration in breathing and ability to swallow. Which at this time is of paramount importance to our family. Having been diagnosed with type 3 SMA we never thought that we would have to witness SMA taking so much from our grandchild.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I believe that cost effectiveness is indescribably difficult to quantify and too much of the decision has been based on the economic modelling of QUALY's and ICER's, which the evidence points out is an inadequate method of measuring impact. How can these models express the fear of being unable to breath or eat without

chocking, being unable to lift a drink, dress yourself, turn in bed, use the bathroom unaided, have personal privacy put into the hands of strangers?
How can QUALY'S AND ICER's express the loss of a professional career to become a parent carer or the lack of progression in a career for a carer due to the commitment needed to give exceptional care to a member of the family? What is the value of coping with the difficulty of organising a holiday, visiting friends and family, having an evening out as a couple? The loss of a retirement for grandparents as they willingly divert their energy to supporting families affected by SMA? These things cannot be given a monetary value. What is the value given to the relentless form filling ensuring systems are in place, fighting for your child's rights and care needs? None of these can be quantified.
In the evidence it was agreed that the cost benefits analysis should be against Best Standard Care. It is proven this only gives care and does not reverse or halt the progression of SMA. I do not believe that in the present circumstances this is a reasonable comparison.
Now there are two treatments approved, the comparison should be between the effectiveness, accessibility and clinical outcomes of treatments, in the various scenarios of SMA, which as stated in the evidence are inadequately classified.
The choice of treatment should be at the discretion of the lead clinical team. They have the information available about the clinical condition of the patient, the efficacy of the available treatments and can assess the progression of SMA and prescribe the appropriate treatment. Whilst treatment is ongoing, they are in the best position to evaluate the success / failure of the chosen treatment.
The addition of Risdiplam adds to a suite of treatments available to clinicians. This could mean that the most suitable treatment is selected for individual patients. It should therefore not add to the cost of treating individual SMA patients because treatments will not run concurrently. It has already been decide that all patients who have SMA should receive treatment under the MAA and this should be implemented within a year, Having competition also drives down costs and increases competition for further innovation and cost reduction. The addition of Risdiplam will speed up rollout which has been significantly adversely affected by COVID restrictions on in patient care.
In the last few years two treatments have been approved by NICE expensive but both may completely alter the course of SMA. Yet the cost of Risdiplam has been compared with Best Standard Care. Recently NICE gave approval for all patients with SMA to be treated with Spinraza. An acknowledgement that walking is not an endpoint that all will achieve and there are other factors which needing treatment. I am profoundly grateful for this, but we know Spinraza may not be suitable for all and Risdiplam could be a solution to the problems of access to be treated with Spinraza or Zolgensma.
I should like to highlight some of these costs when compared with Spinraza which have not been considered in the evidence.
1 Loss of workdays for parents/ carers
taking the SMA patient for treatment.
2 Loss of school or work days for the SMA patient,
3 Cost of travel to the treatment centre if Spinraza is the only treatment of choice.
4 Cost of the consultants and nurses giving the injection, in our case two consultants will be required because of
spinal surgery.
5 Cost of radiology , and supporting staff
6 Risk of repeated radiology exposure.
7 The possibility of hospitalization after the intrathecal injection because of the distance travelled. So additional loss
of time.

If this treatment is given to younger children, whose symptom have not progressed, it could completely stop the inevitable progression of SMA. Some of the benefits could be.

1 No need for spinal fusion
2 No need for wheelchairs.
3 Reduction in physiotherapist and occupational therapist time
4 Reduction in home adaptations with the associated cost to social services.
5 Cost of external care givers stop

- Are the recommendations sound and a suitable basis for guidance to the NHS?

I do not believe that the cost effectiveness of a treatment, in a civilised developed society, should guide its use, if it is shown to give benefits to those desperately needing treatment.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

I think that the whole debate around SMA treatment. past and present, emphasises on motor milestones, lack of or loss of them. and taken little time to consider the fact that SMA patients are articulate, usually have above average/high IQ and have 'feelings' . They have to work harder than the general population to reach their educational potential as they have spent many hours having physiotherapy, hospital visits for assessments, dealing with colds which turn into major chest infections . Yet despite this they just push on to catch up on lost time. Not once have I read any document which takes into account that people with SMA are just like you and me. They are identified only by their disability not their other abilities. This is a continuing and worrying thread.

It is with great sadness and dismay that the committee have recommended refusal of this innovative treatment for all types of SMA,

- Section 1.2: “SMA is a rare genetic condition and there is an unmet need for effective treatments that could slow disease progression.”

“SMA is a rare genetic condition and there is an unmet need for effective treatments that could slow disease progression.”

The committee recognises that there is a need for treatment of this devastating condition. This need is urgent. People and families living with SMA know the course of the disease is progressive and relentless, choose how high the Best Standard of Care available to them. The progression of SMA leads to the loss of so many abilities, the most devesting result is death. Living with SMA often leads to inability to breath, chew and swallow without assistance, besides removing most motor functions. The people living with SMA have, usually, normal or above normal intelligence and with Best Standard of Care, go to mainstream school, university and follow this with productive and fulfilling lives. SMA strips them of their physical abilities and the prospect of becoming a person who contributes to Society is significantly diminished. Treatment is urgently required to help them reach their full potential. That treatment is available.

- Section 1.2: “There is no evidence on risdiplam for babies with pre-symptomatic SMA. Clinical evidence shows that risdiplam improves motor function in SMA types 1 to 3. Also, there is some evidence suggesting that people with type 1 SMA who have risdiplam live for longer. But there is no direct evidence comparing risdiplam with best supportive care for type 1 SMA. And there is no long-term evidence, so the estimated long-term benefits are highly uncertain.”

Surely this is obvious, they have yet to display symptoms so why would there be any evidence or reason to treat. These children will not be identified until screening for the condition at birth for all babies, Very few babies may be identified if they are younger siblings of children diagnosed with SMA. This is a very low number of the SMA population in the world so difficult to identify and form into a study.
One of the problems for people born with SMA is that their symptoms may not be apparent for several months or years after they are born. Even then the pathway to diagnosis is not smooth with long waits for a diagnosis and often an erroneous diagnosis before the correct diagnosis is made.
"Also, there is some evidence suggesting that people with type 1 SMA who have Risdiplam live for longer. But there is no direct evidence comparing Risdiplam with Best Supportive Care for type 1 SMA."
The most recent evidence on Type 1 SMA, treated with Risdiplam, (Roche virtual event on Key Evrysdi presented at the 2021 CureSMA Annual Meeting 14th June 2021) shows significant gain in motor milestones after 12months of treatment. The milestones reached were compared with WHO milestone achievements and are similar to the world population .
"there is no long-term evidence, so the estimated long-term benefits are highly uncertain."
It will not be know whether improvement will continue unless they continue to receive the treatment. We know that the outcome of Best Supportive Care will be little or no gain in motor function and untimely death. Treating SMA now is 'buying time' for future treatments, which may cost less and have greater effect.

- Section 1.2: “The committee considered a wide range of issues in its decision-making. In particular, it discussed the rarity and severity of SMA, risdiplam's innovative oral administration, uncertainties in the evidence, and whether risdiplam should be considered as an end-of-life treatment.”

"In particular, it discussed the rarity and severity of SMA, risdiplam's innovative oral administration"
The oral administration of Risdiplam, makes it accessible to a larger group of people with SMA. There are several factors which make the administration of Risdiplam preferable to Spinraza.
a Those who have had spinal fusion making intrathecal delivery difficult or impossible.
b Those who live far from centres licenced to deliver Spinraza.
c The complexity of delivery of Spinraza needing highly skilled doctors and technicians.
d Theatre and X-ray time , which could be utilised for other urgent purposes.
e The complications which can occur from intrathecal delivery.
f Time lost from education and work of both the SMA patient and the carer / PA.
g The circulation of the medication in the CNS and the general circulation make this treatment particularly appealing for in people who have swallowing and

breathing difficulties . I understand Spinraza only circulates only in the CNS and improves motor function.
"whether Risdiplam should be considered as an end-of-life treatment."
I am assuming that this refers to babies with SMA type 1, who are now being given the gene therapy Zolgensma. This treatment only is available to babies under the year of 1. There are therefore babies, with SMA type 1, who are predicted to die before the age of 2. These babies currently are not going to have this treatment but may be having Spinraza. It should not be thought that the lives of these children is over if a treatment is available.
I would consider both Risdiplam and Spinraza as "beginning of life" treatment for people with SMA of all types older than 1.

- Section 1.2: “The cost-effectiveness estimates presented are much higher than what NICE usually considers an acceptable use of NHS resources. So, even taking these other factors into account, risdiplam cannot currently be recommended.”

The UK is the Worlds 5th largest economy. Let us not dither over cost. How can we let people live with this devastating condition, which affect all walks of life, whole extended families, as well as the people living with SMA. It comes to families uninvited. Treatments are required now, our family has waited 18 years for this, many families for much much longer. NICE have mechanisms (MAA) for accepting drugs with cost higher then normally considered. Risdiplam is an additional treatment in the armoury for SMA and will not be used concurrently with the treatments already approved. So unless the costs are significantly different to Spinraza should this be an issue? Excluding one treatment, of two available, creating a monopoly for the other treatment.

- Section 2.1

“Risdiplam (Evrysdi, Roche) is indicated for 'the treatment of 5q spinal muscular atrophy (SMA) in patients 2 months of age and older, with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies'."
Risdiplam is already licenced under the EAMS pathway by the MHRA. Why can this access not be opened to all people with SMA who have a clinical need. Is this just a cost issue because the treatment appears to be having a positive effect?”

- Section 2.2

"The list price is £7,900 per 60mg/80ml vial. The company has a commercial arrangement, which would have applied if the technology had been recommended."
The actual pricing of Spinraza and Risdiplam to the NHS is redacted in the documents as ' consumers' we cannot know whether the two treatments are of a comparable price. It is up to the negotiators to finalise an equitable cost of the treatment. Having read all the documents I am assuming that cost is a key barrier to the committees approval.

- Section 3

"The company's unanchored matched adjusted indirect comparison of Risdiplam with best supportive care is acceptable. "

Other treatments are now available. It is known that Best Supportive Care leads only to deterioration. The cost and standards of BSC vary widely would it not now be more appropriate to compare with the other treatments in use. Particularly in reference to method of delivery of the treatment and the possible more beneficial outcomes on breathing and swallowing, a particular concern of SMA patients who have already lost a significant amount of mobility and muscle function.

- Section 3.12

"The patient experts described the importance of maintaining upper limb function because it allows independence. They explained that some benefits were not captured in the available motor function scales because even small improvements were highly valued by patients and made a large difference to health-related quality of life."

Until treatment is available to the wider SMA community we will not find out. What is certain is that these skills will be lost in some patients with advanced motor deterioration. They should be given a chance at maintaining their function.

- Section 3.12: “The patient experts described the importance of maintaining upper limb function because it allows independence.”

This is SO important to members of the SMA community. The importance cannot be emphasised enough. It is the difference between feeding and washing yourself. Using the WC and showering independently, even though you are using a hoist to facilitate this. Writing drawing, baking, using the wheelchair controls are all dependent on upper body and fine motor skills. Brushing teeth, opening packets cutting up food the list goes on. It is these small things, which they face losing, and keep the SMA community fighting for treatment.

- Section 3.13

" The committee concluded that the ERG's approach to including caregiver utility values is consistent with TA588 but neither the company's nor the ERG approach is ideal, so there is substantial uncertainty"
I agree with the uncertainty of including care giver utility values.
How can QUALY’S AND ICER’s express the loss of a professional career to become a parent carer or the lack of progression in a career for a carer due to the commitment needed to give exceptional care to a member of the family? What is the value of coping with the difficulty of organising a holiday, visiting friends and family, having an evening out as a couple? The loss of a retirement for grandparents as they willingly divert their energy to supporting families affected by SMA? Living without a second carer due to the dangers of infecting with COVID to the household. Living with the fear of being ill yourself and unable to care. These things cannot be given a monetary value. What is the value given to the relentless form filling ensuring systems are in place, fighting for your child's rights and care needs? None of these can be quantified.

- Section 3

"The patient experts explained that SMA is a progressive disorder so all patients will experience more severe symptoms over time. "
The treatment of the symptoms of SMA should be decided by need evaluated by the clinical team. Not the type as is currently defined.

- Section 3.1

The generalised description of the symptoms and severity of SMA are difficult to use in practice. The manifestations of SMA have to be dealt with as they present in the individual and cannot only be defined by type . Treatment should not be confined to type , it should be by clinical need and they should have a choice of treatments available to them. .

- Section 3.1

Type 3 SMA is defined as a 'milder' type of SMA this does not always follow. Some of Type 3 patients can develop very severe symptoms of SMA. Scoliosis - requiring surgery, not walking needing to use a motorised wheelchair, upper body weakness , breathing difficulty, swallowing difficulty etc. they can be affected by SMA the same as Type 2 , the symptoms just take longer to develop. Others develop only 'mild' symptoms and can walk propel themselves in a wheelchair, do transfers, sit themselves and undertake most daily functions for a longer period and retain upper body strength and control.
This is not the fault of the clinicians misdiagnosing . It is a deficiency in the knowledge and understanding of how the disease progresses and what other factors are controlling this. For now there is the system of Type 1, 2 3 and 4, but it should not be a system which is used to give or refuse access to any treatment. Access should be available decided on patient symptoms by the clinical team.

- Section 3.1

"The committee understood that risdiplam's marketing authorisation includes types 1 to 3 SMA as currently defined by the SMA classification system and these definitions were also used in the clinical evidence (see section 3.5). The committee acknowledged the limitations of the current SMA classification system but concluded that it had been used in the marketing authorisation and clinical evidence for risdiplam."
It with great relief that the committee understand the limitations of classification and that this treatment, should it be authorised, should be available for all types of SMA according to clinical need.

- Section 3.2

Every family living with SMA is different. Some families have two or three children with the condition. What is common the relentless progress of the condition choose how hard you try to minimise it . Having to fight the 'system' for support, adaptations and treatment. The interminable form filling to justify your family's particular needs. The anticipation of ' how bad can it get'. The financial worries as you have to give up work to care. The loss of your identify as you become ' the carer '. The juggling of family with children who are not ' disabled' . The negotiations with the education system as you wish your bright child to go to main stream school and university. The toll this all takes on your own physical health and wellbeing is immeasurable.

- Section 3.3

In the evidence it was agreed that the cost benefits analysis should be against Best Standard Care. It is proven this only gives care and does not reverse or halt

the progression of SMA. I do not believe that in the present circumstances this is a reasonable comparison.
Now there are two alternative treatments approved, the comparison should be between the effectiveness, accessibility and clinical outcomes of the treatments, in the various scenarios of SMA, which as stated in the evidence are inadequately classified. The choice of treatment should be at the discretion of the lead clinical team. They have the information available about the clinical condition of the patient, the efficacy of the available treatments and can assess the progression of SMA and prescribe the appropriate treatment. Whilst treatment is ongoing, they are in the best position to evaluate the success / failure of the chosen treatment.

- Section 3.5

If the clinical studies had shown that there was no meaningful gains from administering the treatment the drug company would not have submitted Risdiplam for approval.

- Section 3.5

"The committee concluded that it had not seen any evidence for people who have had nusinersen and agreed to take this into account when making its recommendations"
There are a group of TYPE 3 SMA patients who were denied accessibility to Nusinersen. Recently this decision was reversed. The delay of receiving treatment has been compounded by COVID restrictions. During the delay of almost 2years their mobility and strength has deteriorated . These patients are desperate to receive a treatment. They are generally older, understand completely the implications of the progressive nature of the condition. Many of these patients will have had spinal fusion for scoliosis and access to give intrathecal injection will be complex, difficult and is some cases impossible. these people need an alternative route of administration of treatment. Risdiplam gives this option and would speed up treatment, without the significant strain on the NHS of administering Spinraza .

- Section 3.7

"The committee concluded that it had not seen any evidence for people who had pre-symptomatic SMA and agreed to take this into account when making its recommendations. "
Until there is genetic testing at birth for SMA there will only be a few children who are diagnosed pre -symptomatically with SMA . Only children with older siblings, with a diagnosis of SMA , are screened. Therefore the number of known pre-symptomatic children will be small. Pre-symptomatic diagnosis of adults would require whole population screening and therefore the accumulation of evidence in pre symptomatic groups is unlikely to be currently obtained.

- Section 3.8

Improvements in motor function would be welcome but we are aware stabilization of symptoms at this point is a realistic expectation for some patients who have significant deterioration of motor movement.. This would give great comfort to those who are having or facing difficulties with breathing speaking and swallowing.

- Section 3.9: “The committee concluded that, although risdiplam would likely provide long-term benefits, the size and nature of these benefits are not known so this is uncertain.”

People with SMA should have the opportunity to explore what the long term benefits may be. They know the course of SMA if no treatment is given.

- Section 3.11

It would seem fair that the stopping rule is based on the clinical criteria and is the subject for discussion with ethic committee, the clinical team, the patient and their family. There are already a number of conditions which are 'untreatable' this type of decision has to be made by the clinician and the patient. It should not be a reason for withholding treatment in the first place.

- Section 3.15

By treating with either Spinraza or Risdiplam . We are 'buying time' for more treatments to be developed and authorised.
In the course of the preparation of application, to NICE, for Risdiplam to be authorised as a treatment for SMA, a gene therapy , Zolgensma, has been authorised, in the UK, for type 1 SMA patients. This is may be a game changer and in the future we may not see any people needing any other treatment. There will be more of these game changers under development but for now we just have two possibilities for people over the age of one. These should not be denied to the SMA community.

- Section 3.16: “The committee noted that, using its preferred assumptions, the most plausible ICER for type 1 SMA was much higher than £50,000 per QALY gained. For types 2 and 3 the ICER was much higher than £30,000 per QALY gained (the company considers the ICERs to be confidential so they cannot be reported here). The committee concluded that the ICERs for risdiplam are above £50,000 per QALY gained.”

The clinical effectiveness of Risdiplam, albeit to stabilise, not cure, gives such hope. HOPE is a word not used in the household of families with SMA , vocabulary often. Hope that they will not choke whilst sharing a meal . Hope that they will not be admitted to hospital with chest infections. Hope they will not need night-time ventilation. Hope their mother (as it usually is) will get a full night’s sleep. Hope that they will successfully attend University. Hope that they will be a sharing and contributing member of Society, able to visit friends’ homes and navigate the inaccessible world Society has created. These are just a small example of things this treatment gives SMA families hope for. If treatments are not approved all this hope for many families is diminished.
I believe that cost effectiveness is indescribably difficult to quantify and too much of the decision has been based on the economic modelling of QUALY's and ICER's, which the evidence points out is an inadequate method of measuring impact. How can these models express the fear of being unable to breath or eat without chocking, being unable to lift a drink, dress yourself, turn in bed, use the bathroom unaided, have personal privacy put into the hands of strangers?

- Section 3.18: “The clinical and patient experts agreed that an alternative treatment option is needed. The committee concluded that risdiplam is innovative, but no data had been presented for benefits relating to its

innovative nature that had not already been captured in the economic analyses."

In the last few years two treatments have been approved by NICE expensive but both may completely alter the course of SMA. Yet the cost of Risdiplam has been compared with Best Standard Care. Recently NICE gave approval for all patients with SMA to be treated with Spinraza. An acknowledgement that walking is not an endpoint that all will achieve and there are other factors which needing treatment. I am profoundly grateful for this, but we know Spinraza may not be suitable for all and Risdiplam could be a solution to the problems of access to be treatment.
I should like to highlight some of these costs when compared with Spinraza which have not been considered in the evidence.
1 Loss of workdays for parents/ carers taking the SMA patient for treatment.
2 Loss of school or work days for the SMA patient,
3 Cost of travel to the treatment centre if Spinraza is the only treatment of choice.
4 Cost of the consultants and nurses giving the injection, in our case two consultants will be required because of
spinal surgery.
5 Cost of radiology , and supporting staff
6 Risk of repeated radiology exposure.
7 The possibility of hospitalization after the intrathecal injection because of the distance travelled. So additional loss of time.
If this treatment is given to younger children, whose symptom have not progressed, it could completely stop the inevitable progression of SMA. Some of the benefits could be.
1 No need for spinal fusion
2 No need for wheelchairs.
3 Reduction in physiotherapist and occupational therapist time
4 Reduction in home adaptations with the associated cost to social services.
5 Cost of external care givers stop

- Section 3.20: "The committee acknowledged that the population eligible for risdiplam has serious disabilities. It acknowledged and considered the nature of the eligible population as part of its decision making."

So what is the reason for refusing approval of Risdiplam ? Cost? If so why can the drug not be approved using a MAA?

- Section 3.21: "It acknowledged and considered whether any adjustments to its normal considerations were needed to take into account the rarity and severity of the disease. The decision making takes into account the rarity and severity of the disease."

So why is treatment being denied?

- Section 3.22: "The committee also acknowledged other factors including the innovative nature of risdiplam, the nature of the eligible population and the rarity and severity of SMA (see sections 3.18 to 3.21). Taking all this into account, the committee concluded that risdiplam is not likely to be a cost-effective use of NHS resources for treating SMA. It noted that the company had not submitted a proposal for a managed access agreement and concluded that risdiplam cannot be recommended for routine commissioning in the NHS at this time."

So, is the bottom line that this drug is not cost effective under the rule of £50,00 per QUALY?
NICE have power under the MAA to authorise this treatment just as it has done for Spinraza.
Having two treatments, which could be life changing, for people living with SMA is a bonus. It provides an option for treating clinical and social need.
The treatments are both high cost but denying one authorisation will not drive down the overall cost of treating SMA.

Approving Risdiplam will free up hospital space to treat some of the huge waiting list for many illnesses and conditions of people who can only receive their treatment in a clinical setting.
Having treatment available to use at home, at the discretion of the clinical team, will speed up the rollout of this vital treatment. It will also avoid any delays to treatment which may be caused by another wave of COVID overwhelming our NHS.

Risdiplam for treating spinal muscular atrophy: A Single Technology Appraisal

Addendum: ERG's comments the company's ACD response

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK
	Aline Navega Biz, Research Associate, ScHARR, University of Sheffield, Sheffield, UK
	Emma Hock, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK
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1. Introduction

This addendum summarises the additional clinical evidence detailed in the company's response to the NICE Appraisal Consultation Document (ACD) for risdiplam[1] and provides a critique of the company's updated economic analyses for Type 1 and Type 2/3 spinal muscular atrophy (SMA). Additional exploratory analyses undertaken by the ERG are also presented.

The company's Appraisal Consultation Document (ACD) response[1] includes:

- A written document which provides an overview of longer-term data from FIREFISH and SUNFISH, as well as supplementary data from JEWELFISH and RAINBOWFISH.[1] The response document also outlines the additional assumptions applied in the company's updated base case models and a summary of the model results. Summaries of longer-term data from FIREFISH and SUNFISH were also available from separate slide decks[2, 3] and a summary document submitted to NICE prior to the release of the NICE ACD.[4]
- Updated versions of the company's executable models for Type 1 and Type 2/3 SMA.
- A summary document which briefly describes the changes applied in the company's updated models.[5]
- An appendix which summarises the results of the company's updated models.[6]

Additional written responses to the ACD were also received from SMA REACH UK, MD UK and one clinical expert.

This addendum is set out as follows. Section 2 summarises the additional clinical evidence presented in the company's ACD response. Section 3.1 presents a summary and critique of the company's post-ACD Type 1 SMA model, together with additional exploratory analyses undertaken by the ERG. Section 3.2 presents a summary and critique of the company's post-ACD Type 2/3 SMA model, together with additional exploratory analyses undertaken by the ERG. Section 4 provides recommendations for further economic analyses of risdiplam.

2. Summary of new clinical evidence and ERG comments

2.1 Additional data from FIREFISH (Type 1 SMA)

The company's ACD response[1] includes longer-term data from the 24-month data-cut of the single-arm FIREFISH study (Type 1 SMA).[2] Key results from the 12- and 24-month data-cuts of this study are summarised in Table 1.

The primary outcome of Part 2 of FIREFISH was the proportion of infants sitting without support (for five seconds) after 12 months of treatment, as assessed in Item 22 of the Bayley Scales of Infant and

Toddler Development – Third Edition (BSID-III) Gross Motor Scale. Just over twice the number of infants were able to attain this milestone at 24 months (25/41, 61%) than at 12 months (12/41, 29%), which represents a clinically meaningful milestone gain when compared with the natural history of Type 1 SMA.

The ERG report[7] focused on the following key secondary outcomes in FIREFISH: proportion of patients able to support weight or stand with support as assessed by the Hammersmith Infant Neurologic Examination, Module 2 (HINE-2); proportion of patients able to bounce while assessing the walking item of the HINE-2; proportion of patients alive without permanent ventilation (event-free survival [EFS]), and overall survival (OS). A slightly greater proportion of infants were able to support weight or stand with support (11/41, 27%) and bounce (2/41, 4%) as assessed by the HINE-2 at 24 months than at 12 months (9/41, 22%, and 1/41, 2%, respectively). Similar proportions of patients were alive (38/41, 93%) and alive without permanent ventilation (34/41, 83%) at 24 months compared with 12 months (38/41, 93%, and 35/41, 85%, respectively), suggesting that survival and EFS gains were largely maintained between 12 and 24 months of follow-up. These represent clinically meaningful benefits when compared with the natural history of Type 1 SMA.

Additionally, data presented in the Darras *et al.* slide deck[2] indicate that one of the 41 (2%) patients in Part 2 of FIREFISH had progressed to the 'cruising' milestone of the HINE-2 'walking' item, which represents a milestone not previously reached in this patient population.

Patients, carers and a clinician who responded to the NICE ACD emphasised the value of bulbar function in patients with SMA. New efficacy data from Part 2 of FIREFISH suggest that improvements in bulbar function were maintained between 12 and 24 months, with 35/41 (85%) of patients able to feed orally at 24 months.

Table 1: Clinical efficacy summary, FIREFISH Part 2; 12 & 24 month outcomes (reproduced from the FIREFISH and SUNFISH efficacy summary submitted to NICE 29th April 2021[4])

Endpoint	12 Months* (n=41)	24 Months† (n=41)
Primary efficacy endpoint		
Number / proportion (90% CI) of patients sitting without support for 5 seconds (BSID-III) at timepoint	12/41 29%	25/41 61%
Secondary efficacy endpoints		
Motor function and development milestones		
Number / proportion (90% CI) of patients who achieve a score of 40 or higher in the CHOP-INTEND at timepoint	23/41 56%	31/41 76%
Number / proportion (90% CI) of motor milestone responders^ as assessed by the HINE-2 at timepoint	32/41 78%	35/41 85%
Number / proportion (90% CI) of patients able to support weight or stand with support[c] as assessed by the HINE-2 at timepoint	9/41 22%	11/41 27%
Number / proportion (90% CI) of patients able to bounce while assessing the walking item of the HINE-2 at timepoint	1/41 2%	2/41 4%
Survival and ventilation-free survival		
Number / proportion (90% CI) of patients alive without permanent ventilation[$] at timepoint (90% CI)	35/41 85%	34/41 83%
Number / proportion (90% CI) of patients alive at timepoint	38/41 93%	38/41 93%
Nutrition		
Number / proportion (90% CI) of people with the ability to feed orally at timepoint	34/41 83%	35/41 85%
Exploratory efficacy endpoints		
Motor function and development milestones		
Number / proportion (90% CI) of patients sitting without support for 30 seconds (BSID-III) at timepoint	7/41 17%	18/41 44%
Number / proportion (90% CI) of patients who achieve a score of 50 or higher in the CHOP-INTEND at timepoint	8/41 20%	18/41 44%
Number / proportion (90% CI) of patients who achieve a score of 60 or higher in the CHOP-INTEND at timepoint	0/41 0%	4/41 10%
Healthcare utilisation		
Number of hospitalisations[#] per patient-year at timepoint (90% CI)	1.30	0.94

**Data cut-off: 14 Nov 2019. †Data cut-off: 12 Nov 2020. ^ Infant classed as responder if more motor milestones show improvement than show worsening. Improvement defined as a ≥2-point increase in ability to kick (or maximal score) or ≥1-point increase in head control, rolling, sitting, crawling, standing or walking. Worsening defined as ≥2-point decrease in ability to kick (or lowest score) or ≥1-point decrease in head control, rolling, sitting, crawling, standing or walking. [$] No permanent ventilation defined as no tracheostomy or BiPAP ≥16 hours per day continuously for >3 weeks or continuous intubation >3 weeks, in the absence of, or following the resolution of, an acute reversible event. [#]Hospitalizations include hospital admissions ≥1 night.*
BSID-III, Bayley Scales of Infant and Toddler Development, Third edition; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination, Module 2;

2.2 Additional data from SUNFISH (Type 2/3 SMA)

The company's ACD response[1] also includes longer-term data from the 24-month data-cut of the SUNFISH randomised controlled trial (RCT) (Type 2/3 SMA). These data are from the risdiplam arm of the RCT (n=120), as no patient received placebo after 12 months. A summary of key endpoints from the 12- and 24-month data-cuts of this study are summarised in Table 2.

The primary outcome of Part 2 of SUNFISH was motor function, assessed by change from baseline in Motor Function Measure - 32 Items (MFM-32) Total Score at 12 months. The longer-term clinical evidence reported in the company's ACD response suggests that gains made at 12 months (mean change 1.65, standard deviation [SD] 4.70) were maintained and slightly improved at 24 months (mean change 1.83, SD 5.59).[3]

The ERG report[7] focused on the following secondary outcomes in SUNFISH: change from baseline in Hammersmith Functional Motor Scale Expanded (HFMSE) total score; adverse events (AEs) and changes in fine motor skills from baseline to 12 months (from the Revised Upper Limb Module [RULM], MFM-32 and the SMA Independence Scale [SMAIS]). The longer-term data suggest that gains made at 12 months were maintained at 24 months for the patient-reported SMAIS total score, and maintained and slightly improved at 24 months for the HFMSE total score, RULM, and caregiver-reported SMAIS total score. Changes in MFM-32 Domain 3 scores (which focus on upper limb function) were not reported in the 24-month follow-up data.

Table 2: Clinical efficacy summary, SUNFISH Part 2; 12 & 24 month outcomes (reproduced from the FIREFISH and SUNFISH efficacy summary submitted to NICE 29th April 2021[4])

Endpoint	12 Months* (n=120)	24 Months† (n=120)
Primary efficacy endpoint		
Mean change (SD) in MFM-32 Total Score from Baseline to timepoint	1.65 (4.70)	1.83 (5.59)
Secondary efficacy endpoints		
Patients with change in MFM-32 ≥ 3 (Baseline to timepoint), n (%)	44 38.3%	37 32.2%
People with change in MFM-32 ≥ 0 (Baseline to timepoint), n (%)	80 69.6%	67 58.3%
Mean change (SD) in RULM Total Score from Baseline to timepoint	1.91 (3.87)	2.79 (4.38)
Mean change (SD) in HFMSE Total Score from Baseline to timepoint	1.81 (3.68)	2.15 (5.28)
Mean change (SD) in caregiver-reported SMAIS score from Baseline to timepoint	1.68 (4.95)	2.73 (5.16)
Mean change (SD) in patient-reported SMAIS Total score from Baseline to timepoint	0.95 (3.78)	0.82 (4.83)

**Data cut-off: 30 Sep 2020. †Data cut-off: 6 Sep 2019.*
HFMSE, Expanded Hammersmith Functional Motor Scale – Expanded; RULM, Revised Upper Limb Module; MFM32, 32-item Motor Function Measure; SD, standard deviation; SMAIS, SMA Independence Scale.

2.3 Additional data from JEWELFISH (previously-treated SMA)

New exploratory 12-month data from the open-label, single-arm JEWELFISH study of patients previously treated with RG7800, nusinersen, olesoxime and onasemnogene abeparvovec (AVXS-101)[8] suggest that patients previously treated with nusinersen or AVXS-101 experienced a rapid >2-fold increase in survival motor neuron (SMN) protein levels from baseline, which was sustained over time, with a safety profile similar to that of treatment-naïve patients.[1] The ERG notes the company has not presented an economic analysis of risdiplam in previously-treated patients.

2.4 Additional data from RAINBOWFISH (patients with genetically diagnosed pre-symptomatic SMA)

The company's ACD response[1] also reports new preliminary 12-month efficacy data from the open-label, single-arm Phase II RAINBOWFISH study for patients with genetically diagnosed pre-symptomatic SMA.[9] Five patients had been treated for ≥12 months at the time of the preliminary analysis. Of these infants, four (80%) attained the maximum Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) score of 64, and four (80%) attained the maximum HINE-2 score of 26. Thus, all five attained milestones of head control, sitting, rolling, and crawling by 12 months, and four (80%) were able to stand unaided and walk independently, with one standing with support and one attaining 'bouncing' from the 'walking' milestone. Overall, risdiplam was well tolerated. These data appear promising; however, the ERG notes that the data presented in the ACD response are preliminary, relate to a small number of participants, and are non-comparative in nature. In addition, the company has not presented an economic analysis of risdiplam for patients with pre-symptomatic SMA.

2.5 Areas of uncertainty

While the additional data presented in the company's ACD response[1] look favourable towards risdiplam, uncertainties remain. Although the natural history of SMA is known, none of the new data reported are from comparative studies. Another key uncertainty is that although patients in FIREFISH[2] demonstrated a further stage on the walking milestone at 24 months ('cruising') than at 12 months (for which the highest attained walking milestone was 'bouncing'), this was only attained in one patient, and it is unclear if any patients would have progressed to walking independently. It is also uncertain how long gains made on risdiplam will be maintained for, which has implications for the development of treatment discontinuation criteria.

3. Summary and critique of company's post-ACD models

3.1 Type 1 SMA model

3.1.1 Overview of changes to Type 1 model

The company's updated Type 1 SMA model includes five sets of amendments:

(1) The inclusion of updated 24-month data on transition probabilities, EFS and OS for the risdiplam group from FIREFISH.[2]

(2) The inclusion of a treatment discontinuation rule for patients who have not reached the sitting state by the treatment benefit plateau timepoint (66 months).

(3) The inclusion of additional assumptions regarding utility values, including an additional utility gain for patients achieving/maintaining upper limb function (applied to the not sitting and sitting states in the risdiplam group) and further patient disutilities associated with SMA complications (applied to non-sitters and patients on permanent ventilation [PV] in both treatment groups, with a greater net utility loss for best supportive care [BSC]). An additional utility gain is also applied to caregivers of patients achieving/maintaining upper limb function.

(4) The inclusion of additional costs associated with SMA complications (applied to non-sitters and patients on PV in both treatment groups, with a greater net cost for BSC).

(5) The inclusion of updated caregiver disutility calculations whereby caregiver quality-adjusted life year (QALY) losses for both groups are included up to the point of mean OS in the BSC group (10.23 years), but are largely excluded thereafter. A separate analysis is also presented which includes absolute caregiver QALYs (as per the company's original approach in the CS[10]).

The company has not revised its existing Patient Access Scheme (PAS) since the first Appraisal Committee Meeting (discount = [redacted] reduction from the list price).

3.1.2 Company's post-ACD model results - Type 1 model

The company's updated base case results for Type 1 SMA are presented in Table 3; these include results for two base case scenarios. "Company's base case 1" applies a caregiver disutility approach (capped at 10.23 years), whilst "Company's base case 2" applies the absolute caregiver QALY approach used in the company's original model.[10] The incremental cost-effectiveness ratios (ICERs) generated using these two approaches are estimated to be [redacted] and [redacted] per QALY gained, respectively. The ERG notes that these ICERs are considerably lower than the ERG's preferred estimates based on the 12-month data-cut of FIREFISH.[11] The company's ACD response[1] includes the results of a third analysis for the Type 1 population which caps the lifetime QALY loss for caregivers of risdiplam-treated patients in each individual health state at the QALY loss for that state in the BSC group. The ERG does not consider this analysis to be meaningful; hence, it is not discussed further in this addendum.

Table 3: Company's updated base case results - Type 1 SMA model

Option	LYGs*	QALYs - patients	QALYs carers	Costs	ICER (patients)	ICER (patients + carers)
Company's base case 1 - caregiver disutilities capped by mean BSC OS (10.23 years)						
Risdiplam	30.50	8.55	-3.90	[redacted]	-	-
BSC	10.21	-1.86	-3.91	[redacted]	-	-
Incremental	20.29	10.41	0.01	[redacted]	[redacted]	[redacted]
Company's base case 2 - absolute caregiver QALYs (as per company's original base case[10])						
Risdiplam	30.50	8.55	25.34	[redacted]	-	-
BSC	10.21	-1.86	5.44	[redacted]	-	-
Incremental	20.29	10.41	19.91	[redacted]	[redacted]	[redacted]

LYG - life year gained; QALY - quality adjusted life year; ICER - incremental cost-effectiveness ratio; BSC - best supportive care
** Undiscounted*

3.1.3 Detailed description of changes applied to company's Type 1 SMA post-ACD model and ERG critique

This section summarises each amendment applied in the company's updated Type 1 SMA model together with comments from the ERG. The ERG notes that all of the changes applied in the company's post-ACD model favour the risdiplam group. With the exception of the new data from FIREFISH,[2] these changes are all based on assumptions rather than evidence.

Model amendment 1: Inclusion of 24-month data from FIREFISH

The company's post-ACD model includes an updated transition matrix and updated EFS and OS models for the risdiplam group based on the 24-month data from FIREFISH.[2] As FIREFISH is a single-arm study, no additional data are available to inform outcomes for the BSC group. The updated model also includes a structural amendment which means that risdiplam-treated patients can transition to the walking health state in every cycle; previous iterations of the model assumed that Type 1 SMA patients could not gain the ability to walk until Month 18 (from age ~2 years).

ERG commentary on updated data from FIREFISH:

- The probability that patients can transition from standing to walking in every cycle reflects a structural assumption which differs from previous versions of the model. No justification is given for this amendment and it is not described in the company's ACD response.[1] However, this amended assumption affects few patients.
- The company's ACD response[1] states *"The 24-month data have been incorporated into the type 1 model so that it is informed by longer-term efficacy data for risdiplam."* No further details are provided in the ACD response regarding how this has been done. The ERG believes that the company has updated the multi-state model to estimate transition probabilities and has re-fitted parametric survival models for EFS and OS using the longer-term data from FIREFISH.[2] Based on the inclusion of these longer-term data, the model-predicted proportion of risdiplam-treated patients who reach the standing or walking states by 66 months is higher

than in the ERG's preferred model at technical engagement (TE) (maximum proportion of patients reaching standing or walking: company's post-ACD model[1] - 43%; ERG-preferred model[7] - 27%). Model-predicted OS for the risdiplam group is also improved using the 24-month data-cut because (a) the updated exponential OS model applied to non-standing states has a lower hazard rate than the previous model fitted to the 12-month data, and (b) more patients reach the standing and walking states, which are assumed to have comparatively lower mortality risks. The extent of this improvement in model-predicted OS is shown in Figure 1 (solid black line versus dashed black line).

- The company's model estimates OS for BSC by applying the inverse of the hazard ratio (HR) from the company's matching-adjusted indirect comparison (MAIC) to the parametric OS model fitted to the FIREFISH data. The previous iteration of the Type 1 SMA model predicted a mean OS for BSC of 4.88 years (Figure 1, grey dashed line). As the longer-term FIREFISH data suggest improved OS for risdiplam, and BSC outcomes are modelled as being conditional on OS for the risdiplam group, mean OS for BSC is also substantially increased. The post-ACD model predicts a mean OS for BSC of 10.21 years, with 10% of patients still alive at age 35 years (Figure 1, solid grey line). The ERG does not consider the model-predicted OS for the BSC group to be clinically plausible and notes that this an artefact of the company's modelling approach rather than the availability of additional data for BSC. Mean OS for the BSC group is a particularly important driver of the ICER (see Section 3.1.4).
- As discussed in the ERG report,[7] the early onset model in TA588 predicted a mean OS duration for BSC of 2.14 years.[12] This is considerably lower than the company's Type 1 SMA model.

Figure 1: Modelled OS from company's post-ACD model and ERG-preferred model at TE

Model amendment 2: Discontinuation rule

The company's post-ACD model includes a treatment discontinuation rule at 66 months for risdiplam-treated patients in the non-sitting and PV states. This discontinuation rule is assumed to have no impact on subsequent risks of mortality or on patients' health-related quality of life (HRQoL). Transition probabilities are also unaffected by the discontinuation rule because patients are already assumed to remain in PV until death, and because no risdiplam-treated patient is assumed to gain milestones after the treatment benefit plateau.

ERG commentary on updated assumptions:

- The company's ACD response[1] states *"Roche would like to emphasise that the discontinuation criteria are implemented in the models as a proxy for the purposes of Committee decision-making, and do not fully reflect how discontinuation criteria would be applied in clinical practice"* The ERG does not consider it meaningful to assess the cost-effectiveness of a medicine based on a discontinuation rule which does not reflect how it will be used in clinical practice. As highlighted by the company, the modelled discontinuation rule impacts on very few Type 1 SMA patients (<3% of all patients starting treatment with risdiplam) and it has a minimal impact on the ICER. The ERG believes that it would be more appropriate to develop revised discontinuation criteria which: (a) reflect discontinuation criteria that would be used in clinical practice and (b) result in a more economically attractive value proposition for risdiplam.
- The discontinuation rule is applied at the plateau timepoint (66 months) for patients who are in the non-sitting and PV health states. This is implemented by cutting the costs of the drug whilst

assuming no loss of health benefits. Specifically, risdiplam-treated non-sitters are assumed to have an indefinite reduction in mortality risk compared with BSC-treated non-sitters, despite having discontinued treatment. The ERG believes that this is a strong assumption.

- Similarly, the treatment-dependent utility values and costs of SMA complications applied in the post-ACD model (discussed in model amendments 3 and 4) continue to be applied after patients have discontinued risdiplam. This implies that the assumed utility gains associated with achieving/maintaining upper limb function and the costs and utility losses avoided through reducing the incidence of SMA complications (severe scoliosis, respiratory problems and bulbar dysfunction) are retained indefinitely, despite patients no longer receiving risdiplam. The ERG believes this is another strong assumption. However, given the limited number of patients who are assumed to discontinue, the impact on the ICER is likely to be small.

Model amendment 3: Additional utility gains and losses

The company's post-ACD model includes the following amendments to the patient and carer utility values:

(a) An additional utility gain of 0.20 is applied to all risdiplam-treated patients in the non-sitting and sitting states. This is intended to reflect the benefits of risdiplam in enabling patients to gain/maintain upper limb function. This value is higher than the values applied in the previous iterations of the model (utility gains of 0.05 and 0.10 applied to non-sitters and sitters in ERG Additional Sensitivity Analysis 1,[7] based on Thokala *et al*.[13]).

(b) An assumed caregiver utility gain of 0.05 is applied for caregivers of risdiplam-treated patients in the non-sitting and sitting states. This is intended to reflect the benefit to caregivers of risdiplam-treated patients gaining/maintaining upper limb function.

(c) Further patient disutilities have been included to reflect negative HRQoL impacts associated with SMA complications of respiratory support (disutility=-0.07, from SUNFISH[14]), severe scoliosis (disutility=-0.09, from SUNFISH[14]) and bulbar dysfunction (disutility=-0.17, from Lloyd *et al*.[15]). These disutilities are added to the patient health state utility values from TA588,[12] based on the assumption that these complications apply to 100% of BSC-treated patients and 50% of risdiplam-treated patients in the non-sitting and PV states in all model cycles.

The resulting utility values applied in the company's post-ACD model are summarised in Table 4.

Table 4: Summary of patient and carer utility values applied in company's updated Type 1 SMA model

Health state	ERG-preferred model[7] (both treatment groups)	Company's post-ACD model[1]		
		Risdiplam	BSC	Treatment-specific utility gain in state (risdiplam vs BSC)
Patient utility values				
(i) Not sitting	0.10	0.14	-0.23	0.36
(ii) PV	-0.02	-0.18	-0.35	0.16
(iii) Sitting	0.20	0.40	0.20	0.20
(iv) Standing	0.70	0.70	0.70	0.00
(v) Walking	0.85	0.85	0.85	0.00
*Caregiver utility values**				
(i) Not sitting	0.48	0.53	0.48	0.05
(ii) PV	0.48	0.48	0.48	0.00
(iii) Sitting	0.63	0.68	0.63	0.05
(iv) Standing	0.77	0.77	0.77	0.00
(v) Walking	0.92	0.92	0.92	0.00

ERG - Evidence Review Group; ACD - Appraisal Consultation Document; BSC - best supportive care

ERG commentary on updated assumptions:

- The ERG's main concern regarding the health state utility values applied in the post-ACD model is that they no longer reflect the values elicited from clinical experts by Biogen which were used in the final early onset model in TA588.[12, 16] Whilst it is unclear what the experts were asked during Biogen's original elicitation exercise, the ERG considers it likely that the estimates already include impacts relating to bulbar dysfunction, scoliosis and respiratory support associated with the non-sitting and PV health states for patients receiving BSC. The inclusion of further disutilities for SMA complications will therefore likely result in double-counting. The ERG also believes that it is inappropriate to apply a further disutility for respiratory support to the PV state, as these patients are, by definition, already receiving respiratory support.
- The company's post-ACD model assumes that 100% of surviving BSC-treated patients who cannot sit incur disutilities from SMA complications in every model cycle. The ERG considers that this assumption is unlikely to be clinically realistic.
- Whilst the ERG considers the achievement and maintenance of upper limb function to be a relevant issue for consideration, there is uncertainty regarding: (i) how many risdiplam-treated patients would achieve these gains; (ii) how long the gains would last, and (iii) the impact of these gains on patient (and potentially caregiver) HRQoL. In the absence of evidence, it is unclear whether the magnitude of the additional utility gains applied in the company's updated model are reasonable.
- As highlighted in the previous section, the treatment-specific utility values shown in Table 4 are applied in every model cycle, irrespective of whether the patient is still receiving risdiplam. The ERG considers this to be a strong assumption.

Model amendment 4: Additional costs associated with bulbar dysfunction, respiratory support and severe scoliosis

The company's post-ACD model includes additional costs associated with treating bulbar dysfunction, respiratory support and severe scoliosis, assuming that these complications apply to 100% of BSC-treated patients and 50% of risdiplam-treated patients in the non-sitting and PV health states. The unit costs and frequencies of each complication were taken from NHS Reference Costs[17] and the Roche Burden of Illness study,[18] respectively. The proportions of risdiplam- and BSC-treated patients affected by these complications are based on assumptions.

Table 5: Costs of treating SMA complications applied in company's post-ACD Type 1 SMA model

Complication	Unit cost	Frequency per cycle	Percentage of risdiplam patients affected	Percentage of BSC patients affected
Respiratory support	£1,570	0.46	50%	100%
Bulbar dysfunction	£2,285	0.17	50%	100%
Severe scoliosis	£4,015	0.04	50%	100%

BSC - best supportive care

ERG commentary on updated assumptions:

- The ERG believes that costs associated with these complications are already reflected in the cost estimates from Biogen's real-world evidence (RWE) survey, as resources relating to all three complications are mentioned as key cost drivers in the Biogen addendum which describes this study.[12] As such, including these additional costs will likely result in double-counting.
- As detailed in the previous section, patients on PV are already receiving respiratory support; hence, including an additional cost will likely result in double-counting.
- The company's post-ACD model assumes that the reduction in the proportion of patients incurring these costs is maintained indefinitely, irrespective of whether patients are still receiving risdiplam. The ERG considers this to be a strong assumption.
- The company's additional cost assumptions are inconsistent with those applied in the final models used to inform TA588.[16]

Model amendment 5: Updated carer disutility approach

The ERG's preferred approach to modelling caregiver QALY impacts is the caregiver disutility approach.[7, 19] Under this approach, carer QALY losses are calculated as a function of: carer disutilities (with greater caregiver losses associated with worse patient health states); the distribution of patients across the alive health states in each cycle (i.e. the model trace); the proportion of surviving patients; a bereavement-related disutility, and the number of caregivers per patient (2.2 caregivers per Type 1 SMA patient). This approach reflects positive caregiver impacts as a consequence of patients reaching improved health states and a lower bereavement-related QALY loss due to improved survival, as well as negative impacts due to extending OS without providing a cure, which increases the duration over which the caregiver burden applies.

The company's post-ACD model ("Company's base case 1") adopts a similar type of caregiver disutility approach as that described above, albeit with some additional assumptions:

(a) Caregiver disutilities are applied in both treatment groups up to a timepoint of 10.23 years; this timepoint is approximately equal to mean OS for the BSC group in the company's post-ACD model. No bereavement-related disutility is applied during this period.

(b) Beyond the timepoint of 10.23 years, the model applies a constant bereavement disutility of -0.04 for the BSC group for all subsequent cycles, based on Song *et al*.[20] In the risdiplam group, no further disutility is applied to caregivers until 30.58 years (approximately equal to mean OS for the risdiplam group); a bereavement-related disutility is subsequently applied in all model cycles.

The net QALY loss over time predicted by the company's capped caregiver disutility approach is illustrated in the lower portion of Figure 2. The upper portion of the plot shows modelled OS for reference. The ERG notes that whilst the plot indicates similar caregiver QALY losses over time for both treatment groups, the factors contributing to these losses differ between the groups. In the risdiplam group, the caregiver QALY losses are driven by patients being in better health states but more patients being alive, whereas in the BSC group, caregiver QALY losses are driven by patients being in the worst health states but fewer patients are alive (hence, fewer caregivers lose QALYs).

Figure 2: Plot of caregiver QALYs and model-predicted OS

The company's ACD response[1] also includes the results of an analysis which applies the company's original absolute caregiver QALYs approach[10] ("Company's base case 2"). A bereavement-related disutility is also applied in this analysis.

Estimates of the cost-effectiveness of risdiplam versus BSC for each of these two approaches are shown in Table 3.

ERG commentary on updated assumptions:

- As described in the ERG report[7] and the ERG's technical engagement (TE) response,[19] the ERG does not consider the assumptions which underpin the company's absolute caregiver QALY approach to be appropriate. These arguments are not repeated here. The NICE ACD[21] also states that the Committee did not accept this approach. Therefore, the ERG believes that the results of "Company base case 2" should be disregarded. The subsequent discussion relates to the company's capped caregiver disutility approach, as applied in "Company's base case 1".
- ERG understands that the company's approach is intended to reflect the concern described in the ACD[21] that the Appraisal Committee *"did not agree that including carer quality of life would result in fewer QALYs being accrued by carers when risdiplam extends survival"*. However, the ERG believes that it is inevitable that a treatment which extends survival for disabled patients with extensive caregiver needs, but which does not provide a full cure, will result in further caregiver burden during the additional survival time afforded by that treatment. Therefore, the ERG believes that it appears conceptually inconsistent to suggest that a chronically disabling disease will impact on caregivers up to some timepoint, but not beyond it. Adopting a position which includes some, but not all, of the relevant caregiver burden in this case may inadvertently set a precedent for other appraisals of treatments which extend OS but do not provide a full cure.
- Irrespective of the appropriateness of the principle, the ERG does not believe that the company's model is able to adequately address the Committee's concern. The company's model adopts a cohort-level state transition approach, which estimates the proportion of patients who are alive over time, rather than survival for pairs of patients with and without risdiplam. As such, the model cannot isolate the additional period of time over which patient survival is extended by risdiplam and caregiver QALY losses should not be counted. The company's approach sets the time cap equal to the mean OS duration for BSC; this would be a reasonable approximation of additional OS afforded by risdiplam if all BSC patients died very quickly (e.g. if there were no long-term survivors). However, this is not the case, as the company's model predicts that 24% of BSC-treated patients are still alive when the cap is applied (see Figure 2). If the intended principle is to exclude caregiver QALY losses incurred due to greater survival in the risdiplam group, there should be no impact on the outcomes for the BSC group. However, the company's approach markedly reduces caregiver QALY losses in both groups (BSC QALY losses with cap = -3.91; BSC QALY losses without cap = -6.26). Importantly, the company's capping approach also ignores the differences in the distributions of patients across the model health states and the associated caregiver impacts between the treatment groups.

Consequently, the ERG does not believe that the company's estimates of capped incremental QALY losses are meaningful.

- The ERG also notes that the bereavement-related QALY loss is underestimated in both groups because it only reflects bereavement impacts for one caregiver, whereas 2.2 caregivers are assumed per surviving SMA patient before the cap. The ERG believes that bereavement-related QALY losses, if included, should be applied at every timepoint proportional to the probability of survival and should reflect the same number of caregivers assumed whilst patients are alive.
- As discussed in the ERG report and the TE response, the final TA588 models applied a caregiver disutility approach without a cap.[12] For the sake of consistency of decision-making, it may be preferable to apply a similar set of assumptions. However, in the Highly Specialised Technology (HST) appraisal of onasemnogene abeparvovec (ID1473), caregiver HRQoL impacts were included only as a scenario analysis and were not included in the base case.[22]
- Overall, the ERG believes that the most coherent approach would be either: (a) to value positive and negative caregiver impacts fully, including some judgement from the Appraisal Committee regarding the impact of bereavement on carer HRQoL, or (b): to exclude caregiver effects from the risdiplam models altogether.

3.1.4 Additional exploratory analyses presented by the ERG

Exploratory analysis - methods

This section presents additional exploratory analyses using the company's post-ACD Type 1 SMA model. These analyses focus on demonstrating the impact of including the 24-month data from FIREFISH[2] in isolation of other model amendments and addressing the problem regarding the implausible predicted mean OS for BSC resulting from the company's modelling approach. The ERG undertook six scenario analyses using the company's Type 1 SMA model, as described below.

EA1: ERG preferred model at TE, 12-month data, no discontinuation rule, no additional utility gains, SMA complications excluded, ERG carer disutility approach excluding bereavement-related disutility. This analysis reflects the ERG's preferred scenario at TE based on the 12-month data-cut of FIREFISH[2] and provides a starting point for the ERG's other exploratory analyses.

EA2: ERG preferred model at TE, 24-month data, no discontinuation rule, no additional utility gains, SMA complications excluded, ERG carer disutility approach excluding bereavement-related disutility. This analysis is the same as EA1, but includes the updated transition probabilities, EFS and OS models for the risdiplam group from the 24-month data-cut of FIREFISH.[2] Other additional assumptions included in the company's post-ACD model are not included.

EA3: ERG preferred model at TE, 24-month data, no discontinuation rule, no additional utility gains, SMA complications excluded, ERG carer disutility approach excluding bereavement-related disutility, BSC OS = 4.88 years. This analysis is the same as EA2, but mean OS for the BSC group is shrunk to 4.88 years (the mean estimate from the ERG's preferred model at TE). This scenario was implemented by applying a lower HR for OS (risdiplam versus BSC) of 0.04425.

EA4: ERG preferred model at TE, 24-month data, no discontinuation rule, no additional utility gains, SMA complications excluded, ERG carer disutility approach excluding bereavement-related disutility, BSC OS = 2.14 years. This analysis is the same as EA2, but mean OS for the BSC group is shrunk to 2.14 years (the mean estimate from the final early onset SMA model in TA588[12]). This scenario was implemented by applying a lower HR (risdiplam versus BSC) for OS of 0.03865.

EA5: Company's post-ACD base case 1, including all additional model changes, company's capped carer disutility approach, BSC OS = 4.88 years

This analysis is the same as the company's post-ACD "base case 1", but mean OS for the BSC group is shrunk to 4.88 years.

EA6: Company's post-ACD base case 1, including all additional model changes, company's capped carer disutility approach, BSC OS = 2.14 years

This analysis is the same as the company's post-ACD "base case 1", but mean OS for the BSC group is shrunk to 2.14 years.

ERG exploratory analysis - results

The results of the ERG's exploratory analyses are presented in Table 6. Based on the ERG's preferred model at TE, applying the 24-month data-cut from FIREFISH[2] substantially reduces the ICER for risdiplam (EA2 - ICER= [redacted] per QALY gained). However, as discussed in Section 3.1.3 (Model amendment 1), this is partly a consequence of the increased OS for BSC, which the ERG considers implausible. EA3 indicates that if mean OS for the BSC group is shrunk to 4.88 years (the estimate from the ERG's preferred analysis at TE), the ICER increases to [redacted] per QALY gained (EA3). If mean OS for BSC is shrunk further to reflect the modelled estimate in TA588,[12] the ICER increases to in excess of [redacted] per QALY gained (EA4). Applying the same reductions in BSC OS to the company's updated "base case 1" results in ICERs which are in excess of [redacted] per QALY gained, irrespective of whether caregiver QALYs are included in the analysis (EA5 and EA6). All of these estimates are considerably higher than the company's updated base case ICERs ([redacted] to [redacted] per QALY gained).

Table 6: ERG exploratory analyses – Type 1 SMA model

Option	LYGs*	QALYs - patients	QALYs carers	Costs	ICER (patients)	ICER (patients + carers)
EA1: ERG preferred model at TE, 12-month data from FIREFISH						
Risdiplam	21.68	4.77	-6.68	[redacted]	-	-
BSC	4.88	0.02	-3.14	[redacted]	-	-
Incremental	16.8	4.75	-3.54	[redacted]	[redacted]	[redacted]
EA2: ERG preferred model at TE, 24-month data from FIREFISH						
Risdiplam	30.47	7.14	-7.32	[redacted]	-	-
BSC	10.21	0.01	-5.49	[redacted]	-	-
Incremental	20.26	7.13	-1.83	[redacted]	[redacted]	[redacted]
EA3: ERG preferred model at TE, 24-month data from FIREFISH, BSC OS = 4.88 years						
Risdiplam	30.47	7.14	-7.32	[redacted]	-	-
BSC	4.88	0.06	-2.83	[redacted]	-	-
Incremental	25.59	7.08	-4.49	[redacted]	[redacted]	[redacted]
EA4: ERG preferred model at TE, 24-month data from FIREFISH, BSC OS = 2.14 years						
Risdiplam	30.47	7.14	-7.32	[redacted]	-	-
BSC	2.14	0.09	-1.46	[redacted]	-	-
Incremental	28.33	7.05	-5.86	[redacted]	[redacted]	[redacted]
EA5: Company's post-ACD base case 1, 24-month data from FIREFISH, BSC OS = 4.88 years						
Risdiplam	30.50	8.55	-2.68	[redacted]	-	-
BSC	4.88	-0.90	-2.29	[redacted]	-	-
Incremental	25.62	9.45	-0.39	[redacted]	[redacted]	[redacted]
EA6: Company's post-ACD base case 1, 24-month data from FIREFISH, BSC OS = 2.14 years						
Risdiplam	30.50	8.55	-1.67	[redacted]	-	-
BSC	2.14	-0.40	-1.86	[redacted]	-	-
Incremental	28.36	8.95	0.20	[redacted]	[redacted]	[redacted]

EA - exploratory analysis; TE - technical engagement; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ERG - Evidence Review Group; BSC - best supportive care; OS - overall survival

3.2 Type 2/3 SMA model

3.2.1. Overview of changes to Type 2/3 model

The company's updated Type 2/3 SMA model includes similar amendments to the Type 1 model:

(1) The inclusion of updated 24-month data for the risdiplam group from SUNFISH.[3]

(2) The inclusion of a treatment discontinuation rule for patients who have not reached the sitting unsupported state by the treatment benefit plateau timepoint (26 months).

(3) The inclusion of additional assumptions regarding patient utilities, including an increased utility gain for patients achieving/maintaining upper limb function (applied to non-standers in the risdiplam group) and further disutilities associated with SMA complications (applied to patients who cannot sit unsupported in both treatment groups, with a greater net utility loss for BSC). An additional utility gain is also applied to caregivers of patients achieving/maintaining upper limb function.

(4) The inclusion of additional costs associated with SMA complications (applied to patients who cannot sit unsupported in both treatment groups, with a greater net cost for BSC).

(5) The inclusion of a caregiver disutility approach. A cap on the duration over which caregiver disutilities apply is not applied in the company's base case for the Type 2/3 SMA population.

3.2.2 Company's post-ACD model results - Type 2/3 model

The company's ACD response[1] presents three sets of results from the Type 2/3 SMA model: (i) an updated base case, which values caregiver QALY impacts using the caregiver disutility approach (excluding any cap for the duration over which these impacts are counted); (ii) a scenario analysis using the caregiver disutility approach with a caregiver-related bereavement disutility and a cap on the duration over which caregiver QALY losses are counted (hereafter referred to as "Scenario analysis A"); and (iii) a scenario analysis using the company's original absolute caregiver QALYs approach[10] ("Scenario analysis B"). Scenario Analysis B assumes 2.2 caregivers for patients who cannot sit; the other two analyses assume 3 caregivers for these patients. The results of these analyses are presented in Table 7.

The company's ACD response[1] reports an updated base case ICER for risdiplam versus BSC of [redacted] per QALY gained. The scenario analyses suggest ICERs ranging from [redacted] to [redacted] per QALY gained. These ICERs are considerably lower than the ERG's preferred estimates based on the 12-month data-cut of SUNFISH (ERG-preferred ICER at TE=[redacted] per QALY gained).

Table 7: Company's updated base case results - Type 2/3 model

Option	LYGs*	QALYs - patients	QALYs carers	Costs	ICER (patients)	ICER (patients + carers)
Company base case - caregiver disutilities (no cap), 3 caregivers for non-sitters						
Risdiplam	50.60	14.11	-2.25	[redacted]	-	-
BSC	43.77	1.19	-10.06	[redacted]	-	-
Incremental	6.83	12.91	7.81	[redacted]	[redacted]	[redacted]
Scenario analysis A - caregiver disutilities capped by mean BSC OS (43.75 years) plus bereavement-related disutility, 3 caregivers for non-sitters						
Risdiplam	50.60	14.11	-2.21	[redacted]	-	-
BSC	43.77	1.19	-9.35	[redacted]	-	-
Incremental	6.83	12.91	7.13	[redacted]	[redacted]	[redacted]
Scenario analysis B - Absolute caregiver QALYs (as per company's original base case[10]), 2.2 caregivers for non-sitters						
Risdiplam	50.60	14.11	42.42	[redacted]	-	-
BSC	43.77	1.19	33.25	[redacted]	-	-
Incremental	6.83	12.91	9.16	[redacted]	[redacted]	[redacted]

LYG - life year gained; QALY - quality adjusted life year; ICER - incremental cost-effectiveness ratio; BSC - best supportive care
** Undiscounted*

3.2.3 Detailed description of changes applied to company's Type 2/3 SMA post-ACD model and ERG critique

This section summarises the amendments applied in the company's updated base-case analysis for the Type 2/3 SMA model together with comments from the ERG. With the exception of the additional data from SUNFISH,[3] these model amendments favour risdiplam and are based on assumptions rather than evidence.

Model amendment 1: Inclusion of 24-month data from SUNFISH

The company's post-ACD model includes an updated transition matrix for the risdiplam group based on the 24-month data from SUNFISH.[3] No additional randomised data are available for BSC. The OS models have not been updated as these were based on data from external sources.

ERG commentary on updated data from SUNFISH:

- The company's ACD response[1] states that *"Results from the 24-month data cut of the SUNFISH trial demonstrate the continued efficacy of risdiplam, with further improvements in key endpoints recorded in comparison to the 12-month data"* and that *"The 24-month data have been incorporated into the type 2/3 model so that it is informed by longer-term efficacy data for risdiplam."* No further details are provided in the ACD response regarding how this has been done. The ERG assumes that the updated transition matrix has been derived by updating the company's original multi-state model.
- Based on the inclusion of these longer-term data, the impact on the model-predicted proportions of risdiplam-treated patients who reach the standing or walking states is minor (maximum proportion of patients reaching standing or walking: company's post-ACD model[1] - 15%; ERG-preferred model[7] - 13%). The inclusion of these new data has a minimal impact on model-predicted OS and QALYs for the risdiplam group. Overall, the isolated impact of including these additional data (without additional assumptions) on the ICER is small (shown later in Table 9).

Model amendment 2: Discontinuation rule

The company's post-ACD model includes a treatment discontinuation rule at 26 months for risdiplam-treated patients in the non-sitting and sitting supported states. This discontinuation rule is assumed to impact on costs and transition probabilities, with treatment effect waning applied linearly such that the probabilities equal those for BSC after 120 months (10 years) following discontinuation. Discontinuation is not assumed to impact on the mortality risks applied within the model health states. The assumptions employed in the Type 2/3 SMA model differ from those in the Type 1 SMA model.

ERG commentary on updated assumptions:

- The ERG's concerns about modelling a discontinuation rule which will not apply in clinical practice, as described in Section 3.1.3, also apply to the Type 2/3 SMA model. The discontinuation rule has a more pronounced impact on the ICER for risdiplam in the Type 2/3 SMA model than the Type 1 SMA model, as more risdiplam-treated patients discontinue treatment (~16%).

- Whilst it is reasonable to assume that previously accrued motor milestones may be lost following discontinuation, there is uncertainty around the time period over which this will occur. The 10-year period applied in the model might be considered optimistic.
- The model assumes that patients who cannot sit independently and who have discontinued risdiplam have the same mortality risk as those who are still on treatment. The ERG considers this to be a strong assumption.
- As with the Type 1 SMA model, the treatment-dependent utility values and costs of SMA complications included in the post-ACD model are also applied after patients have discontinued risdiplam. The ERG believes this is another strong assumption.

Model amendment 3: Additional utility gains and losses

The company's post-ACD model for Type 2/3 SMA includes similar amendments to patient and caregiver utility values as those described for the Type 1 model. The same patient and caregiver utility gains related to achieving/maintaining upper limb function are applied to the not sitting and sitting states. The disutilities for SMA complications are applied to patients who cannot sit without support. The resulting utility values applied in the company's post-ACD model are summarised in Table 4.

Table 8: Summary of patient and carer utility values applied in company's updated Type 2/3 SMA model

Health state	ERG-preferred model[7] (both treatment groups)	Company's post-ACD model[1]		
		Risdiplam	BSC	Treatment-specific utility gain in state (risdiplam vs BSC)
Patient utility values				
(i) Not sitting	0.20	0.24	-0.13	0.36
(ii) Sitting (supported)	0.40	0.44	0.07	0.36
(iii) Sitting (unsupported)	0.50	0.70	0.50	0.20
(iv) Standing	0.70	0.70	0.70	0.00
(v) Walking	0.85	0.85	0.85	0.00
*Caregiver utility values**				
(i) Not sitting	0.70	-0.17	-0.22	0.05
(ii) Sitting (supported)	0.77	-0.09	-0.14	0.05
(iii) Sitting (unsupported)	0.84	-0.02	-0.07	0.05
(iv) Standing	0.92	0.00	0.00	0.00
(v) Walking	0.92	0.00	0.00	0.00

ERG - Evidence Review Group; ACD - Appraisal Consultation Document; BSC - best supportive care

ERG commentary on updated assumptions:

The ERG's main concerns regarding the company's amendments to the patient and carer utility values described for the Type 1 SMA model (see Section 3.1.3) also apply to the Type 2/3 SMA model. The issue relating to potential double-counting of benefits for patients on PV does not apply to the Type 2/3 model.

Model amendment 4: Additional costs associated with bulbar dysfunction, respiratory support and severe scoliosis

The company's post-ACD model includes additional costs associated with treating bulbar dysfunction, respiratory support and severe scoliosis for patients in the not sitting and sitting supported states. These assumptions are the same as those for the Type SMA 1 model, except that different frequencies of use of each resource type are applied.

ERG comments on updated assumptions:

The ERG's concerns regarding the Type 1 model also to the Type 2/3 model. The issue relating to double-counting costs for PV does not apply to this model.

Model amendment 5: Updated carer disutility approach

The company's post-ACD model for Type 2/3 SMA applies the caregiver disutility approach employed in the ERG's preferred analysis.[19] The ERG's concerns regarding the implementation of a cap for caregiver disutilities and the company's absolute caregiver QALY approaches apply to Scenario analyses A and B. However, these do not have a substantial impact on the ICER in this population.

3.2.4 Additional exploratory analyses presented by the ERG

This section presents additional exploratory analyses using the company's post-ACD Type 2/3 SMA model. These analyses focus on demonstrating the impact of including the longer-term data from SUNFISH[3] in isolation of other model amendments and addressing some of the company's modelling assumptions of additional benefits for risdiplam. The ERG undertook four exploratory analyses using the company's Type 2/3 SMA model, as described below.

EA1: ERG preferred model at TE, 12-month data, no discontinuation rule, no additional utility gains, SMA complications excluded, ERG carer disutility approach, no bereavement-related disutility. This analysis reflects the ERG's preferred scenario at TE based on the 12-month data-cut of SUNFISH[3] and provides a starting point for the ERG's other exploratory analyses.

EA2: ERG preferred model at TE, 24-month data, no discontinuation rule, no additional utility gains, SMA complications excluded, ERG carer disutility approach, no bereavement-related disutility. This analysis is the same as EA1, but includes the transition matrix for risdiplam derived using the 24-month data from SUNFISH.[3] Other additional assumptions for risdiplam included in the company's post-ACD model are excluded from this analysis.

EA3: ERG preferred model at TE, 24-month data, no discontinuation rule, utility gains for upper limb function included, SMA complications excluded, ERG carer disutility approach, no bereavement-related disutility. This analysis is the same as EA2, but includes additional utility gains related to patients achieving/maintaining upper limb function in the non-standing states (additional patient utility gain=0.20, additional caregiver utility gain=0.05).

EA4: ERG preferred model at TE, 24-month data, no discontinuation rule, higher utility gain for upper limb function included, SMA complications excluded, ERG carer disutility approach, no bereavement-related disutility. This analysis is the same as EA3, but includes a higher utility gain for patients achieving/maintaining upper limb function in the non-standing states (additional patient utility gain=0.30, additional caregiver utility gain=0.05).

ERG exploratory analysis - results

The results of the ERG's exploratory analyses are presented in Table 9. The ERG notes that these estimates are all considerably higher than the company's updated base case analysis (ICER = [redacted] per QALY gained). Based on the ERG's preferred model at TE, applying the 24-month data from SUNFISH[3] increases the ICER to [redacted] per QALY gained (EA2). The inclusion of additional patient and caregiver utility gains associated with achieving/maintaining upper limb function by patients who cannot stand reduces the ICER to [redacted] per QALY gained (EA3). Increasing the magnitude of the additional utility gain for patients to 0.30 reduces the ICER to [redacted] per QALY gained.

Table 9: ERG exploratory analyses – Type 2/3 SMA model

Option	LYGs*	QALYs - patients	QALYs carers	Costs	ICER (patients)	ICER (patients + carers)
EA1: ERG preferred model at TE, 12-month data from SUNFISH						
Risdiplam	50.30	11.42	-3.60	[redacted]	-	-
BSC	43.77	5.98	-10.06		-	-
Incremental	6.53	5.44	6.45		[redacted]	[redacted]
EA2: ERG preferred model at TE, 24-month data from SUNFISH						
Risdiplam	50.60	11.39	-3.80	[redacted]	-	-
BSC	43.77	5.98	-10.06		-	-
Incremental	6.83	5.41	6.26		[redacted]	[redacted]
EA3: ERG preferred model at TE, 24-month data from SUNFISH plus utility gains for achieving/maintaining upper limb function (patient gain=0.20; caregiver gain=0.05)						
Risdiplam	50.60	15.01	-1.75	[redacted]	-	-
BSC	43.77	5.98	-10.06		-	-
Incremental	6.83	9.03	8.30		[redacted]	[redacted]
EA4: ERG preferred model at TE, 24-month data from SUNFISH plus utility gains for achieving/maintaining upper limb function (patient gain=0.30; caregiver gain=0.05)						
Risdiplam	50.60	16.83	-1.75	[redacted]	-	-
BSC	43.77	5.98	-10.06		-	-
Incremental	6.83	10.85	8.30		[redacted]	[redacted]

EA - exploratory analysis; TE - technical engagement; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ERG - Evidence Review Group; BSC - best supportive care; OS - overall survival

4. Recommendations for further economic analyses of risdiplam

As discussed throughout this addendum, the ERG has several concerns regarding the reliability of the results obtained from the updated economic models submitted as part of the company's ACD response.[1] The ERG is unable to fully resolve these issues, as several relate to the value proposition offered by the company, or require judgements to be made by the Appraisal Committee. Table 10 presents recommendations from the ERG on how these issues might be addressed within future iterations of the company's economic models of risdiplam.

Table 10: ERG recommendations for addressing outstanding issues in company's risdiplam models (Type 1 and Type 2/3 SMA)

Aspect of economic analysis	ERG recommendations
(1) Inclusion of longer-term data on the effectiveness of risdiplam	• Ensure that the inclusion of longer-term data for risdiplam does not lead to implausible model-predicted outcomes for BSC (Type 1 SMA model only)
(2) Discontinuation criteria	• Reconsider discontinuation criteria applied in the model which: o Are clinically acceptable to patients and clinicians; o Are operationally feasible for the NHS; o Reflect how risdiplam is expected to be used in clinical practice (e.g. discontinuing treatment in patients with repeated worsening and/or in those requiring PV[1]); o Result in a better value proposition for risdiplam. • Reconsider the plausibility of assumptions of sustained benefits after discontinuing treatment.
(3) Inclusion of HRQoL gains associated with upper limb function	• In the absence of any evidence to inform the magnitude of utility gains for patients achieving/maintaining upper limb function, the ERG is unsure what might be considered a reasonable assumption • Ensure that the net impact of any assumed additional health benefit on overall utility for model health states is plausible • Consider how many patients will accrue these benefits, their duration and the impact of discontinuation • An expert elicitation exercise to obtain estimates of overall health state utility values for risdiplam-treated patients may be helpful
(4) Inclusion of impacts of SMA complications avoided	• Apply any expected benefit and/or cost-saving in the risdiplam group only • Ensure that the net impact of any assumed additional health benefit on overall utility for model health states is plausible • Consider how many patients will accrue these benefits, their duration and the impact of discontinuation • An expert elicitation exercise to obtain estimates of overall health state utility values for risdiplam-treated patients may be helpful
(5) Caregiver QALYs	• Either fully quantify positive and negative impacts on caregiver HRQoL, or do not consider them at all • Adopt a consistent position on caregiver QALYs for both model populations

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