NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nusinersen for treating spinal muscular atrophy [ID1069]

The following documents are made available to the consultees and commentators:

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

2. **Additional question circulated to consultees and commentators post ACD release**

3. **Consultee and commentator comments on the ACD and additional question circulated post ACD release from**:
   - Biogen
   - Muscular Dystrophy UK
   - Spinal Muscular Atrophy Support UK & SMA Trust (joint response)
   - TreatSMA
   - British Paediatric Neurology Association
   - SMA Reach

   A "no comments" response was received from the Department of health and Social Care

4. **Comments on the ACD and additional question circulated post ACD release from experts:**
   - Dr Adnan Manzur, Consultant Neuromuscular Neurologist – Clinical Expert, nominated by Biogen and SMA Reach
   - Elizabeth Lockley, Patient Expert – nominated by SMA Trust

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

6. **Biogen Appendix 1: Additional Clinical Data**

7. **Biogen Appendix 2: Cost-effectiveness model revisions and updated results**

8. **Evidence Review Group (ERG) commentary on company's ACD response – Addendum**

9. **Company additional evidence from Biogen**

10. NICE clarification questions to the company on their additional evidence

- **ERG request to the company on sub-models**
- **Company response to ERG request on sub-models**
- **ERG additional clarification questions**
- **Company response to ERG additional clarification questions**

11. Evidence Review Group critique company additional evidence

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

Nusinersen for treating spinal muscular atrophy

Single/Multiple 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 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 determination (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, 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.	**Consultee (company)**	Biogen Idec Ltd.	Biogen appreciate the opportunity to provide comments on the NICE Appraisal Consultation Document (ACD) for nusinersen for treating spinal muscular atrophy (SMA) [ID1069]. Biogen are disappointed that the Appraisal Committee was unable to recommend nusinersen in the ACD, however, we are committed to collaboratively finding solutions that address the remaining uncertainties, mitigate risk to the NHS and ensure that access to nusinersen is managed appropriately without further undue delay. In addition, Biogen believe that several conclusions in the ACD are not an accurate interpretation of the evidence and encourage the Appraisal Committee to reconsider its conclusions, as described in the following comments. To support the comments, Biogen have submitted an appendix containing clinical data that explain the long-term model assumptions. The clinical data also clarify the health benefits beyond the primary trial endpoints of survival and motor function. Furthermore, Biogen have put forward a revised commercial offer for consideration. The revisions reduce the ICERs within ranges that may be deemed cost-effective pending further data collection. In parallel, Biogen are continuing to develop a proposal for a managed access agreement (MAA) for consideration by the committee in October.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a managed access agreement (MAA). Responses to comments on specific sections are made below, alongside the respective comments.
2.	**Consultee (company)**	Biogen Idec Ltd.	Paragraph 1.2 notes that there is an unmet need for effective treatments that could slow disease progression. We are concerned that this recommendation may imply that the unmet need is similar across infantile onset (type I) and later onset (types II and III) SMA. Patients with infantile onset SMA fail to develop any motor milestones and rarely survive to their second birthday without permanent ventilation.(1,2) Standard of care only helps to prolong survival of infantile onset patients through highly invasive tracheotomy or permanent ventilation, and it does not slow or prevent the decline of motor and respiratory function.(3) Therefore, given the rapid functional decline in patients with infantile onset SMA, there is an urgent unmet need for an effective treatment that significantly extends life without permanent ventilation, and allows a child to develop any motor	Thank you for your comment. The section referred to is intended to briefly summarise the decision and rationale which is

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			functions that are not possible with the current standard of care. In contrast, patients with later onset SMA are expected to survive until adults, albeit with a progressive loss of motor function and independence.(4–7) Standard of care is aimed at relieving the symptoms, but it does not slow or prevent the decline of motor and respiratory function.(3) For these patients, the progressive decline and loss of ability can have significant impacts on fundamental daily life activities including self-feeding, turning in bed alone, using the restrooms alone, washing by themselves and perform transfers.(8) Therefore, the major unmet need for patients with later onset SMA is to stabilise or improve the current physical condition of patients in relation to muscle strength, respiratory function and mobility/functionality, improving health-related quality of life (HRQoL) and reducing the dependence on carers.(6,8) It is important that the unmet needs and potential benefits with effective, disease-modifying treatment are defined respectively for the 2 patient populations given the different challenges faced by patients, families and their carers.	covered in more detail in section 3.3 (now section 3.4) of the FAD. See also response to comment 6 below.
3.	**Consultee (company)**	Biogen Idec Ltd.	Paragraph 3.1 illustrates SMA as a spectrum disorder but we are concerned about the way in which the level of motor milestones achieved and survival outcomes for type I and II SMA have been depicted. Type I SMA has been described as severe muscle weakness which affects movement, swallowing and breathing. However, for a true description of the disease severity, the wording should be revised to note the 2 year life expectancy of patients and the failure of patients to develop any new motor milestones after maximal motor milestones are achieved (as described by Farrar et al, 2017).(1) Likewise, patients with type II SMA have been described as being 'severely disabled' and 'unable to walk unaided', which is a generalisation that does not fully reflect the condition. In reality, although these patients survive to adulthood, they still have a shortened life expectancy compared to the general population.(1,9,10) The maximal motor milestone achieved is walking with assistance, although some type II patients only ever achieve sitting unaided before declining.(11) Patients are also at a high risk of developing scoliosis.(11) Therefore, the description should be revised accordingly. Furthermore, it should be noted that patients have normal intelligence and are fully aware of their fate and the limitations of current standard of care.(12). The associated fear of losing abilities and independence imposes a major psychological burden on patients and carers as consistently cited in numerous statements from the patient advisory group submissions.(8,13,14)	Thank you for your comment. The text in section 3.1 (now split into 3.1 and 3.2) of the FAD has been amended. The committee acknowledged the psychological burden that people with SMA experience every day.
4.	**Consultee (company)**	Biogen Idec Ltd.	Paragraph 3.1 mentions that SMA classification is blurred and can be subjective. Although it should be acknowledged that SMA is a spectrum disorder it is still possible to classify patients by maximal motor milestone achieved. Patients may reach milestones at the margins of subtypes, and may be referred to as a severe type II or a mild type I, but are still recognised according to the main subtype.(9) Furthermore, 80% of patients with SMA type I carry 1-2 copies of the SMN2 gene, 82% of patients with SMA type II carry 3 SMN2 copies, and 96% of patients with type III SMA carry 3-4 SMN2 copies.(15) Therefore, SMN2 copy number is also used as a key determinant of disease phenotype and is routinely determined after initial diagnosis to help predict the clinical phenotype.	Thank you for your comment. The committee acknowledged the difficulties faced in the current classification. The correlation

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				between copy number and disease severity, which was the opinion of the clinical experts, is addressed in section 3.5 of the FAD.
5.	**Consultee (company)**	Biogen Idec Ltd.	Paragraph 3.2 notes the impacts of SMA on HRQoL, particularly for carers. However, the methodology for assessing caregivers' quality of life is not well developed and there is little evidence about the impact of SMA on caregivers' HRQoL or other important facets of their lives. For example, the sleep deprivation associated with infants needing to be turned a number of times during the night,(8) can be difficult to capture with available instruments. Furthermore, more than one caregiver may be affected, and this may extend beyond the immediate family. A patient survey conducted in Scotland(6) reported that, out of 19 children and adults with SMA, unpaid care was provided by parents (n=16), grandparents or other relatives (n=11), friends (n=4), a partner (n=1), a son/daughter (n=1) or someone else (relationship not disclosed; n=1). A large proportion of the carers had given up work completely (n=42%) or dropped to part-time (37%) due to their caring responsibilities. As is noted as part of the HTA assessment in Ataluren for Duchenne Muscular Atrophy(16), the ERG accounted for 2 caregivers as part of the economic model. From the patient perspective, the range of impacts on patients' HRQoL of diminished educational opportunities or reduced integration into society are also difficult to capture using available HRQoL measures. In children and young people, general issues surrounding the assessment of HRQoL have been addressed in a number of studies. A systematic review by Vaidya (2018)(17) found that, while the PedsQL instrument used as the basis for calculating quality-adjusted life years (QALYs) in the company submission was the most commonly used tool in SMA, no disease-specific tool had been developed for SMA and there is no measurement tool for very young infants (less than 12 months) with SMA type I. Vaidya and Thompson (2017)(18) suggest that a range of instruments, including disease-specific measures, is likely to be required to inform decision-making. Among SMA types II and III, SMA-Europe member organisations (Rouault et al. [2017)(8)] conducted a survey across Europe to explore the importance from the patient's perspective of daily functions and physical condition for their HRQoL. They concluded that tools were still needed that measure functionality and that can be translated into daily life actions of importance to patients.	Thank you for your comment. The committee heard about and acknowledged the difficulties faced by carers. The text in section 3.2 (now section 3.3) of the FAD has been amended to reflect that multiple carers are affected. Section 3.17 and 3.18 of the FAD acknowledge the difficulty in capturing health-related quality of life in people with SMA and their carers. This uncertainty will be addressed in the MAA.
6.	**Consultee (company)**	Biogen Idec Ltd.	Paragraph 3.3 mentions the unmet need for SMA patients and lack of disease-modifying treatments, however Biogen are concerned that the extent of the unmet need is not clear enough. As highlighted by the patient and clinical experts, current treatments do not affect disease progression. Without access to a disease-modifying treatment, patients not only face the loss of motor function, but also premature death which is expected to	Thank you for your comment. The committee acknowledged the unmet need in people with

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			be, on average, 2 years after diagnosis in patients with type I SMA.(1) Furthermore, as patients with SMA have normal intelligence,(12) they are aware of their fate, and this (along with the symptoms experienced) has a significant impact on HRQoL. The urgency to treat should also be noted. The lack of access to a disease-modifying treatment is a time-critical issue due to the progressive neuronal loss and reduced length of life facing patients.(19) The benefits of earlier treatment of nusinersen have been highlighted through subgroup analyses conducted for the later onset population of CHERISH and the infantile onset population of ENDEAR. In the infantile onset population, earlier and greater motor milestone responses and prolonged survival were observed among patients with shorter disease duration at the start of the study (≤12 weeks) compared to patients with a longer disease duration (>12 weeks), suggesting that on average early treatment with nusinersen may confer a stronger benefit. In CHERISH, nusinersen-treated children who were younger and had shorter disease durations generally showed the greatest improvements in HFMSE from baseline; older children and those with longer disease durations demonstrated stabilisation of HFMSE scores in comparison to a decline seen in the sham arm; this is consistent with the idea that early initiation of treatment may lead to greater improvements. Therefore, it is preferred that the wording is revised to stress the extreme and time-critical extent of unmet need to help put the value offered by nusinersen, a disease-modifying treatment, into context.	SMA. Section 3.3 (now section 3.4) acknowledges that current treatments do not affect disease progression and section 3.1 highlights the shortened life expectancy. The unmet need has also been emphasised the section 'why the committee made these recommendations'. Furthermore, section 3.10 of the FAD now addresses early administration of nusinersen.
7.	**Consultee (company)**	Biogen Idec Ltd.	Paragraph 3.1 and 3.4 stress the lack of evidence in type 0 and IV as well as the potential issues in genetic testing and delays in treatment. The ACD states that "However, the clinical experts stated that gene testing may lead to delays in starting treatment." Biogen are not aware of evidence that gene testing may lead to delays in starting treatment. Diagnostic delays are indeed common in SMA, which may have a negative impact on families; SMA symptoms can vary widely in onset and severity and can resemble other diseases and a lack of awareness or expertise of SMA means that healthcare professionals may often consider other diagnoses before SMA.(20,21) In this respect there have been calls for a new-born screening programme to help speed up the diagnosis of SMA. Biogen are committed to helping improve the early diagnosis of SMA. The ACD also states that "Moreover, they considered the correlation between copy number and disease severity is much less reliable than the clinical classification system in identifying the likely course of SMA"; however as described in comment number 4, SMN2 copy number is also used as a key determinant of disease phenotype in conjunction with the clinical classification system, with neither system being completely robust for what is a spectrum disease.	Thank you for your comment. The potential delays of gene testing in starting treatment was the opinion of the clinical experts. The correlation between copy number and disease severity which is referred

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			The ACD states that "The committee acknowledged that nusinersen should be considered within its marketing authorisation (that is, for all types of SMA) but the company had not presented evidence for type 0 and type 4 SMA." Biogen are pleased that the committee have acknowledged that nusinersen should be considered within its marketing authorisation i.e. for all types of SMA. The company's restricted submission is aligned with available clinical data i.e. in infantile onset SMA (type I) and later onset SMA (type II and III) and ability to conduct an economic analysis. However, it should be noted that types I-III capture the majority of SMA cases; SMA type I, II and III are reported to constitute 60%, 27% and 12% of all SMA cases,(22) respectively; data on type 0 and IV are limited because they are rarely diagnosed. Clinicians have questioned whether type 0 treatment may be futile. Based on the underlying disease pathophysiology and the mechanism of action of nusinersen(23), there is good reason to believe that nusinersen could benefit patients with type IV SMA, however without evidence it is not possible to quantify the size or duration of benefit. Biogen are continuously assessing data generation efforts for the population with type IV SMA.	to in section 3.4 (now 3.5) of the FAD was the opinion of the clinical experts. The company's managed access agreement proposal now excludes type 0 and 4 SMA.
8.	**Consultee (company)**	Biogen Idec Ltd.	Paragraph 3.5 notes that the evidence was suitable for decision making despite its uncertainties. Biogen note that the limitations identified in the ENDEAR and CHERISH trials should be viewed in the context of the difficulties of conducting trials in orphan diseases, with the clinical trial development programme for nusinersen being one of the largest for an orphan indication. Specific limitations with the trial data addressed here are: • a different dosing schedule in the CHERISH trial compared with the marketing authorisation • the (more homogeneous) patient composition of the CHERISH trial compared with clinical practice • the short follow-up periods in the ENDEAR and CHERISH trials In relation to the dosing schedule, the clinical development plan evaluated a range of single and multiple doses of 1 mg to 12 mg of nusinersen. Several different loading dose regimens and 2 different maintenance dose regimens have also been evaluated. This allowed the dosing regimen to be refined over time based upon emerging results from the clinical trials. The licensed dosing is with 4 loading doses on days 0, 14, 28 and 63, with a maintenance dose administered once every 4 months thereafter. In CHERISH, nusinersen was administered using 3 loading doses (on study days 1, 29 and 85), followed by maintenance dosing 6 months thereafter (on day 274). The recommended licensed dose of 12 mg was used in CHERISH. The impact of this and the more homogeneous patient composition of the CHERISH trial compared with clinical practice on the trial results is unknown although they will not necessarily be in nusinersen's favour. It is anticipated that the more intensive loading dose interval used in the licensed dosing vs that used in CHERISH (i.e. 4 vs 3 loading doses and maintenance dose at every 4 months vs 6 months) would not lessen the efficacy of nusinersen in later onset SMA patients (if anything, it may improve efficacy). The short follow-up periods in the ENDEAR and CHERISH trials are due to the extremely positive results at interim analysis	Thank you for your comment. The evidence was considered in the context of a number of factors described in the FAD including the rarity and severity of the disease (see section 3.26). The committee acknowledged the reasons for the differential dosing, the homogenous population and the short follow-up periods. However, as they were unable to determine how these differences would impact on

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			points and the view of independent ethical review committees that it would be unethical to proceed with the trials. While the limitations of the ENDEAR and CHERISH trials are acknowledged in terms of duration of follow-up, subjects in both trials were given the opportunity to join the SHINE study and other studies to additionally provide longer term and real-world evidence to inform decision making. Interim results (30th June 2017) of the SHINE study showed that patients receiving nusinersen in both ENDEAR and SHINE studies had significantly better outcomes than those who were in the sham procedure control group in ENDEAR and in the nusinersen group in SHINE on key endpoints of overall survival and median time to death or permanent ventilation (see Appendix 1). Those continuing with nusinersen in SHINE experienced new improvements in motor milestones (Hammersmith Infant Neurological Examination [HINE-2]) and general motor function (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders [CHOP INTEND]). The analysis showed that improvements in motor milestones are achieved whatever the age of treatment initiation, but benefits are generally greater with early treatment. These findings are also supported by longer-term data from the phase II study CS3A in type I patients, in which patients have been assessed over a 3.5-year treatment period), and the phase I study CS2 and its extension CS12 in type II and III patients (treated for 2.2 years). These studies support the maintenance of effect with long-term treatment beyond the age of 24 months and show the robust nature of the clinical trial programme in this orphan rare disease area.(23)	the results, they considered it important to note these uncertainties (see section 3.5, now 3.6). Longer-term results from SHINE are now summarised in Section 3.9 (now 3.11) of the FAD.
9.	**Consultee (company)**	Biogen Idec Ltd.	Paragraph 3.6 mentions that the ENDEAR trial was stopped early due to the strength of the survival benefit, however Biogen would like to request amendment of the reason for stopping the trial. Overall, the ENDEAR trial was stopped early due to the efficacy observed in the nusinersen group compared to the sham control group and ethical consideration for the infants in the control group.(24) The first primary endpoint was a motor-milestone response (defined according to results on the HINE-2) and the second primary endpoint was event-free survival (time to death or the use of permanent assisted ventilation).(24) Only the first primary endpoint was analysed at the interim analysis, while all the other endpoints were analysed at the final analysis. In the interim analysis, a significantly higher percentage of infants in the nusinersen group than in the control group had a motor-milestone response (21 of 51 infants [41%] vs. 0 of 27 [0%], P<0.001), and this result prompted early termination of the trial.(24) In the final analysis, a significantly higher percentage of infants in the nusinersen group than in the control group had a motor-milestone response (37 of 73 infants [51%] vs. 0 of 37 [0%]), and the likelihood of event-free survival was higher in the nusinersen group than in the control group (hazard ratio for death or the use of permanent assisted ventilation, 0.53; P = 0.005). Overall, the interim results for improvement in motor milestones were so compelling compared to sham procedure that the study was concluded and infants were moved to the open-label extension study SHINE.	Thank you for your comment. Section 3.6 (now section 3.7) of the FAD was amended accordingly.
10	**Consultee (company)**	Biogen Idec Ltd.	Paragraph 3.7 notes that outcomes reported in ENDEAR, such as respiratory function, time on ventilator and hospitalisations cannot be reported because they are academic in confidence (AIC). It is stated that the committee considered these outcomes did not show a substantial benefit and found it counterintuitive that a substantial survival outcome was not associated with a substantial benefit in other outcomes. Due to the small patient population in SMA it is difficult to power multiple trials to test multiple endpoints and hypotheses. ENDEAR and CHERISH were powered and designed to show survival and motor improvement, which they have demonstrated. The trials were not designed to specifically look at respiration; they were not powered to detect differences	Thank you for your comment. Section 3.7 (now section 3.8) of the FAD was amended accordingly.

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			between the groups in respiratory outcomes, which would need a much larger cohort. As we heard in the AC meeting from the NICE elected clinical advisor, it is very difficult to measure respiratory function in infants. Hours on ventilation is the most appropriate scale for infants with SMA, however it is very subjective. In addition, respiratory outcomes would be confounded by the time of year that the therapy was initiated. If rescue of respiratory function had not yet occurred during the winter months in the ENDEAR trial then additional lung tissue damage could have occurred from recurrent severe viral infections. Lung function would also be hampered by frequency and number of aspirations, which is also partially dependent on the gastrointestinal approach adopted for each patient. Despite all the above barriers and confounders listed above statistical benefit on ventilation is still shown with nusinersen therapy (see Appendix 1 Section 1.3). Without prejudging what the committee considers to be a substantial benefit, the trial results show that, in addition to survival benefits, nusinersen also had a beneficial impact in terms of ventilation and hospitalisation. These show that a significantly higher proportion of nusinersen treated patients compared with sham procedure control patients survived without permanent ventilation at the end of the study and, among infants not requiring ventilation support at baseline, a significantly higher proportion in the nusinersen group did not require initiation of ventilation support while on the study (Parsons et al., 2018) (see Appendix 1; section 1.2). Overall time spent hospitalised and time spent hospitalised for respiratory reasons were both significantly lower in the nusinersen group compared with the sham procedure control group (Tulinius et al., 2018) (see Appendix 1; section 1.3). Please note that the AIC label can now be removed from the ENDEAR trial results as they have been the subject of the above conference presentations.	
11	**Consultee (company)**	Biogen Idec Ltd.	Paragraph 3.8 noted that nusinersen significantly improved motor function of children with later onset SMA but it was unclear how this affects survival because there were no deaths during the CHERISH trial. The relationship between motor function and survival is particularly relevant to later onset (type II and III) patients as life expectancy is not reported to be significantly less than that in a normal population. Pulmonary disease, secondary to inspiratory and expiratory muscle weakness, is the primary cause of both morbidity and mortality in patients with type II SMA (Wang et al., 2007). Kaufmann et al. (2012) found that pulmonary and motor function outcomes both declined in patients with types II and III SMA over observation periods exceeding 1 year. However, while nusinersen is associated with an impact in the long term on both motor function and survival, this relationship cannot be quantified from the clinical trials. It should be emphasised that type II SMA encompasses a wide spectrum of patients, with a correspondingly wide range of levels of motor function and of mortality.	Thank you for your comment. Section 3.8 (now section 3.9) of the FAD is a commentary about the available evidence on survival. However, the model for later onset SMA included a survival benefit for this population which the committee accepted.
12	**Consultee**	Biogen Idec	Paragraph 3.9 highlights the uncertainties associated with nusinersen. Although Biogen agree that there are uncertainties in	Thank you for

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	(company)	Ltd.	the absence of data, we are concerned that this uncertainty has been overstated. The nusinersen clinical development programme is the largest body of evidence for an interventional approach in SMA, with over 5 years of data. The mechanism of action of nusinersen combined with the observed data to date, indicates that the effects of nusinersen can be sustained in the long-term. Overall, nusinersen has demonstrated favourable efficacy and tolerability in clinical trials and clinical practice for patients with SMA, with no evidence of a lessening of effect over time. Biogen are committed to collecting long-term data and addressing the surrounding uncertainties. Data from SHINE have recently become available (of which the latest evidence is presented in Appendix 1, section 1.1 (see separate document)), showing the longer-term benefits of nusinersen including improvements in motor function and increased event-free survival in patients followed for nearly 3 years. Following suggestions form the EMA, Biogen is supporting prospective, non-interventional studies (registries) of patients receiving and not receiving nusinersen to provide further evidence of efficacy and safety of the therapy. Biogen are also continuing to develop a proposal for a MAA for consideration by the committee in October.	your comment. The uncertainty about the long-term benefit was the opinion of the clinical experts, the ERG and the committee. Sections 3.7 and 3.11 of the FAD now refer to data from SHINE. Section 3.9 (now section 3.11) notes that the committee considered that long-term benefits were likely, though uncertain. These uncertainties will be addressed in the MAA.
13	**Consultee (company)**	Biogen Idec Ltd.	Paragraph 3.10 noted that the model structure was based solely on motor milestones and that the structure was consistent with the main outcomes of the clinical trials. At the same time, the evidence review group (ERG) explained that motor function was not the only factor affecting HRQoL. The committee concluded that the models had limitations but were suitable for decision making. We concur with the committee that the economic model structures were chosen to be aligned with the main clinical trial outcomes. We also agree with the ERG that motor function is not the only factor affecting HRQoL and argue that a broad perspective on patient outcomes should be taken. HRQoL data collected in the CHERISH trial using a broad-based instrument (the Paediatric Quality of Life Inventory (PedsQL)) were used as the basis for estimating QALYs in infantile and later onset SMA as no HRQoL measures are available for infants. Caregivers completed the questionnaires as proxies where patients were unable to. However, the assessment of HRQoL is extremely difficult in children and young people with SMA for a number of reasons. First, young children undergo dramatic changes in growth and function at different rates, so it is difficult to evaluate the effect of a health intervention.(25) Second, current generic measures, except Health Utility Index Mark 2, are derived from adult populations, so additional attributes	Thank you for your comment. The challenges around HRQoL are addressed in section 3.14 and 3.15 (now sections 3.17 and 3.18) of the FAD. This uncertainty will be addressed in the MAA. Furthermore, the company's approach to reflecting patient and carer utilities

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			relevant to children, for example autonomy, body image, and family relationships, may not be captured by these measures.(25) Conceptually, HRQoL for children, particularly infants, will depend on different factors from those important to adults. Therefore, when used as proxies, caregivers may not represent patients adequately and instead capture their own anxieties due to the illness.(25,26) Currently, there is no generic instrument for measuring HRQoL in infants and children younger than 5, highlighting the challenge of deriving utility values in this population. Young children usually do not have the cognitive ability to understand and complete valuation or even measurement tasks.(25). Although the PedsQL measure is frequently used in SMA, and there is some evidence for its validity, reservations have been expressed about this instrument. Where treatment is expected to improve survival (particularly in early onset) beyond the normal life expectancy of patients with SMA, there is no experience on which to base HRQoL assessments. Therefore, at this moment in time, clinical judgement is the best approach to address the uncertainties in HRQoL. Furthermore, as also described in comments 19 and 20, QALYs are unlikely to capture all the important aspects of HRQoL in these patients. Reducing a patient's life experience to a single number on the EQ-5D scale is unlikely to be sufficiently sensitive to capture all aspects of HRQoL for SMA. For example, ability to communicate and grasp objects will not be detected using generic measures, but these represent important improvements in a child's development. In the absence of directly assessed utilities (e.g. EQ-5D questionnaire), a mapping algorithm was used to convert PedsQL data into EQ-5D but it may not be generalisable specifically to SMA patients. Furthermore, utilities for any given health state are assumed to be constant over time, which is unlikely to reflect real life. Comment 5 describes other factors impacting the HRQoL of patients with SMA, that are not possible to represent through the methods preferred by NICE to estimate QALYs.	has now changed.
14	**Consultee (company)**	Biogen Idec Ltd.	Paragraph 3.11 noted that the assumption underlying the transition probabilities used in the models that those treated with best supportive care could not get better was, according to the ERG, inconsistent with the observed trial data, in which a small proportion of people receiving sham therapy had improvements in symptoms over almost all time periods. On the other hand, clinical experts thought it possible that early onset SMA would progressively worsen if left untreated but that some patients taking nusinersen could worsen. Worsening of some patients treated with nusinersen in clinical practice may reflect the difference between trial populations and the prevalent population with SMA as well as the urgency to treat early to maximise the chances of success. Heterogeneity of response between patients treated with nusinersen is acknowledged. However, the model structure is not designed to have a one to one correspondence between trial patients and the modelled cohort. Beyond the end of trial follow-up, the most appropriate approach was considered to be to use the mean changes for trial patients as a whole. This was supported by a clinical advisory group, and continuing improvements beyond the end of trial follow-up in ENDEAR have been reported in the SHINE study. Recently published data from SHINE (presented in Appendix 1 (see separate document)) show improvements in motor function and increased event-free survival in patients followed for nearly 3 years.	Thank you for your comment. The company's modelling approach has now changed and section 3.11 of the FAD (now section 3.15) has been amended.

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			For patients receiving best supportive care, a number of studies have shown that the natural history of SMA is characterised by a worsening of the condition. Kaufmann et al. (2012) found that motor and pulmonary function declined over time in patients with types II and III SMA, particularly at time points beyond 12 months of follow-up. Mercuri et al. (2016) found a mean decline in Hammersmith Functional Motor Scale Expanded (HFMSE) scores over a 12 month period in patients with types II or III SMA. Type III SMA can be further divided into subtypes IIIa and IIIb. Children with type IIIa and IIIb develop symptoms between 18 months and 12 years and are frequently able to walk at the point of diagnosis. However, although patients with SMA type IIIb have a 97% probability of walking 10 years after diagnosis, the probability reduces to 73% for children with SMA type IIIa.(1) Over a follow-up period of up to 40 years, Zerres et al. (1997) show a decline in the probability of being able to walk in patients with types IIIa and IIIb SMA.	
15	**Consultee (company)**	Biogen Idec Ltd.	Paragraph 3.12 notes that, in better health states, the models apply a similar mortality risk to patients with less severe types of SMA, with the ERG observing that the overall survival benefit of nusinersen was driven mainly by this mortality adjustment and considering it optimistic, as did the committee. While the long-term impact of nusinersen on survival is uncertain, and the assumptions used to model may be considered optimistic, as they were by one of the clinical advisers, the ERG reports that the other clinical adviser thought the survival curves reasonable. Clinical experts support the proposition that the preservation of respiratory muscle function should translate into a long term survival benefit but, in the absence of long term data, quantifying the magnitude of this benefit is challenging. Indeed, the ERG's own preferred analysis adopted the same approach to survival, suggesting that, while this analysis did not address concerns around the plausibility of the company's survival extrapolation, it is a not unreasonable 'base case'. Ultimately, longer term data is needed to assess whether this approach gives realistic survival estimates.	Thank you for your comment. The company's approach to apportioning mortality risk has now changed and section 3.12 of the FAD (now section 3.16) has been amended. This uncertainty will be addressed in the MAA.
16	**Consultee (company)**	Biogen Idec Ltd.	Paragraph 3.13 notes that the ERG considered the patient utilities used in the company's models to lack face validity, preferring a vignette study based on European Quality of Life-5 Dimensions (EQ-5D) assessments by healthcare professionals to the mapping of PedsQL data to EQ-5D. The committee considered that both approaches had serious limitations but that it would take account of both in its decision making. As acknowledged by Biogen, the point raised by the committee illustrates the inherent challenges associated with capturing HRQoL and utility data in SMA, especially for infants and young children and highlights questions around the appropriateness of using a single metric such as the QALY to assess the value of nusinersen. In the absence of HRQoL or utilities available from the ENDEAR trial, the vignette study was undertaken to generate utilities for early onset patients. At the same time, given the limitations (as described in comment 13) of the algorithm mapping PedsQL to EQ-5D for the later onset population, the vignette approach has some advantages if the initial small sample of clinicians in which the study was undertaken can be increased. The impact on the cost-effectiveness results in later onset SMA of using the ERG's approach rather than the company's approach demonstrates the importance to the results of the way in which HRQoL	Thank you for your comment. The company's approach to reflecting patient utilities has now changed and section 3.13 of the FAD (now section 3.17) has been amended. This section comments on the challenges in assessing HRQoL. This

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			and utilities are assessed. In the absence of a well validated SMA-specific HRQoL instrument, consideration needs to be given to the best way of capturing HRQoL within any MAA.	uncertainty will be addressed in the MAA.
17	**Consultee (company)**	Biogen Idec Ltd.	Paragraph 3.14 noted that the ERG had critically appraised the assumptions behind the company's approach to carer utilities but that its proposed alternative was considered by the committee to lack face validity. Biogen agree with the committee that the ERG approach lacks face validity. In infantile onset SMA, the health state with the highest patient utility had lower carer utility than all other states apart from 1 of the 2 states with the joint lowest patient utility (the 2 states had patient utility of -0.24 and carer utilities of 0 and 0.85, respectively). In later onset SMA, the 2 states with the joint highest patient utility had lower carer utility than all other states apart from the 2 with the joint lowest carer utility (both with utility of 0). It is counterintuitive that inclusion of carer QALYs should increase the incremental cost-effectiveness ratios (ICERs) as in the ERG analysis. Currently, the methodology for incorporating carer QALYs into the analysis is underdeveloped and neither the company approach nor the ERG approach provides a satisfactory solution. An alternative method needs to be developed and consideration given to the number of caregivers affected (as was done in the NICE appraisal of ataluren) given the demands placed on families and caregivers by the degree of dependency seen in SMA. Biogen have provided exploratory analyses for caregiver QoL in a separate appendix. Biogen would like to re-iterate the substantial burden on family carers, impacting on their HRQL and posing a substantial economic burden on SMA families, and wider society. A high proportion of working parents with SMA have to reduce or even leave their jobs, leading to financial strain and further impacting on their HRQL(27) A survey of SMA families in Scotland (n=19; n=2 with type I or II, n=17 with type II or III) found that 79% (n=15/19) of the main unpaid carers had to give up work completely or drop to part time.(6) Parents of children with SMA (total of 12 replies across types I-III) reported that they attend 2–6 appointments per month in connection with their child's SMA, and 6 (50%) estimated they spend over 20 hours per month in connection with these appointments.(6) As the disease progresses, patients require more intensive treatments. The impact on carer's lives was also captured in the survey based on representative comments from family carers regarding the challenges of looking after a child with SMA, as follows(6): • Parent of young person age 16 with SMA type II: The biggest challenge in having a child with SMA is learning to adapt your life to meet the needs of your child not just the physical and emotional demands but the financial demands as well as anything needed for a child with a disability comes with a huge price tag. • Parent of child age 2 with SMA type II: Turning 4 times a night and monitoring the ventilation up to ten times a night. We always have to take care of the needs of our baby by ourselves and spend countless hours trying to give them the care (physiotherapy) they should be receiving from professionals by ourselves. • Parent of a young person age 11 with SMA type III: Tiredness, backache, lack of time for myself, lack of time for other child, stress. • Parent of a child age 19 – 35 months with SMA type I / II (specific age not given): At such a young age the biggest concern for us is our mental preparation for physical deterioration and the problems we will face as a family.	Thank you for your comment. The company's approach to reflecting carer utility has now changed and section 3.14 of the FAD (now section 3.18) has been amended. Section 3.3 of the FAD highlights that the committee acknowledged the extreme difficulty that patients, carers and families face due to SMA. This section has been further amended following consultation to emphasise the impact on carers and families.

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			• Parent of a child age 9 with SMA type III: Taking time out of work to attend appointments. Constantly 'pushing' to get what our child needs / not feeling that we are doing enough. Emotional difficulties/distress and extra stress. Extra vigilance, worry and uncertainty about everyday activities and about what the future holds for our child. Challenging to help child be as independent as possible, and to fulfil their potential. Sibling relationship management.	
18	**Consultee (company)**	Biogen Idec Ltd.	Paragraph 3.15 noted the committee's conclusion, taking into account the company's cost-effectiveness estimates and the ERG's estimates (including the exploratory analyses increasing the ICER by up to £200,000 per QALY), that the ICER based on the list price could reasonably be predicted at between £400,000 and £600,000 per QALY but may be higher. A number of factors contribute to a large element of uncertainty in the estimates of cost-effectiveness. These relate to the challenges of demonstrating long term benefits given the early termination, after positive interim findings of the pivotal trials and considering the sparse nature of additional data to aid the extrapolation of survival and their lack of alignment with standards of care in the UK. Other uncertainties relate to the conceptual and practical issues surrounding the assessment of HRQoL and utilities in this patient group and quantifying the impact on carers.	Thank you for your comment. Section 3.15 (now section 3.20) has changed following substantial changes to the model. Furthermore, the recommendations in the Final Appraisal Document (FAD) have changed. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a managed access agreement. This uncertainty will be addressed in the MAA.
19	**Consultee (company)**	Biogen Idec Ltd.	Paragraph 3.17 explains that nusinersen has been recognised as innovative but that these benefits have not been captured. Biogen are pleased that the appraisal committee have recognised the innovation of nusinersen, however they are concerned that the committee feel that the economic analyses have not captured any data to show distinct and substantial benefits relating to the innovative nature of nusinersen. Current standard of care cannot result in improved survival, stabilisation and improvement of motor milestones as shown with nusinersen, which is a clear indication of the innovative nature of the drug. The clinically meaningful improvements in motor	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. Nusinersen is

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			function (for example being able to improve or maintain the ability to self-feed, have a wash independently, use the bathroom independently and perform transfers alone to name but a few), together with significant improvements in event-free survival will help to alleviate the profound physical and psychosocial burden experienced by patients and carers.(13,14,28,29) Biogen believe that due to the conservative-nature of the economic model, it does not fully capture the clinical, psychological and social impact that an efficacious disease-modifying treatment will have on patients with SMA and their carers. As described by McGraw et al "just the difference between not being able to move a finger and being able to move a finger by half an inch can mean the difference between being able to operate a motorized wheelchair or not, and that makes a huge impact on their quality of life and on their ability to be independent".(14) Improvements such as this do not occur in untreated patients as part of the natural history of disease. Furthermore, stabilisation of the disease is also considered to a be clinically significant advance in patients(8) in this progressive disease, and this is also not fully captured in the economic model. As another example, it has recently been reported that ambulatory children treated with nusinersen in the CS2/CS12 study demonstrated improvements in ambulatory function, as determined by the 6-minute walking test (6MWT), with increases in walking distance and stabilisation or decreases in fatigue.(30) While there is no precedent for improvements like these in SMA, changes of ≥30 meters are considered clinically meaningful and thought to impact everyday activities in other paediatric neuromuscular disorders.(31) Decreasing fatigue with corresponding increases in distance walked during the 6MWT may represent a treatment effect. Nusinersen is the only treatment that can change the course of the disease in this manner, and not all of these factors such as improving fatigue have been captured in the economic model. In addition, there are several clinical aspects that were not captured in the nusinersen clinical trials and therefore not the models; it is likely that the innovative benefits of nusinersen will help to mitigate at least some of these. In this way it is likely that the base case for the economic model represents a conservative estimation. These areas include: The clinical trial programme includes pre-symptomatic patients that in a real word setting would be identified by new-born screening (NURTURE). The data show that the greatest improvements in total HINE-2 motor milestones were observed in infants treated with nusinersen in the pre-symptomatic stage of SMA in NURTURE as illustrated in the figure below. However, these results were not included in the economic model, which again shows the conservative nature of the model. 1. Swallow, time it takes to feed child and make up feeds 2. Speech and other forms of communication 3. Weight over/under gain 4. Aspiration frequency 5. Cough and time required for chest physio and cough assist 6. Pain	now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a managed access agreement. Section 3.17 of the FAD (now 3.24) in fact states that 'it was not presented with any data to show distinct and substantial benefits relating to the innovative nature of nusinersen **that have not** been captured in the economic analyses'. In short, the committee felt that the innovative nature was captured in the economic analyses. The text in this section has been clarified. Section 3.17 of the FAD notes committee conclusions that utilities may not have captured added benefits of obtaining

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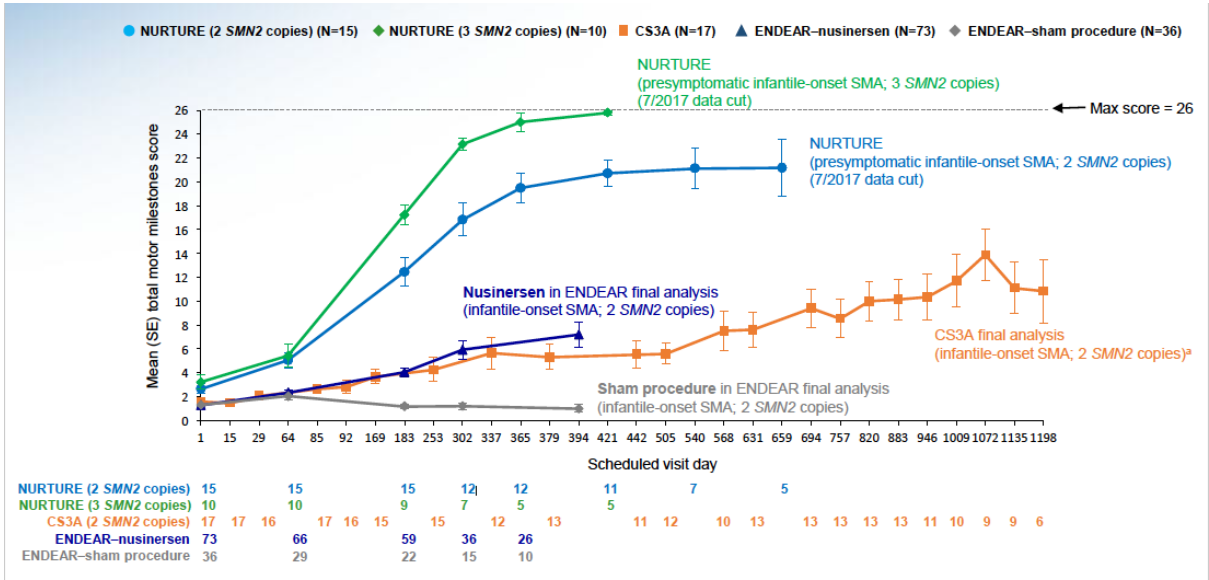
			7. Contracture management / contracture stretching 8. Fracture frequency and management 9. Joint dislocation 10. Gut dysmotility and constipation 11. Pressure sores and their management 12. Phycological impact 13. Impact on siblings and family 14. Frequency of infections 15. Scoliosis 16. Broader lung function tests in older children HINE-2 motor milestone scores across studies  Abbreviations: HINE-2, Module 2 of the Hammersmith Infant Neurological Examination; SE, standard error, SMA, spinal muscular atrophy; SMN, survival motor neuron NURTURE study interim analysis data cut-off date: July 5, 2017. aCS3a end of study data for the cohort of infants with 2 SMN2 copies. Please note all patients in the figure have 2 copies of SMN2 except the green nurture line. This is for clarity of comparison	particular motor skills. The Committee were encouraged by the interim results of NURTURE (the new section 3.10 of the FAD reflects this) and the updated recommendation now include treatment of pre-symptomatic patients in the context of the managed access agreement. The committee discussion the rarity of the disease is covered in section 3.26 of the FAD.

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			Source: Finkel 2018(32) Finally, it should be noted that the availability of nusinersen in England and Wales will help foster investments in drug innovation for patients in other currently underserved rare disease areas. In particular, the development of nusinersen has involved many decades of research into optimising antisense technology - this technology now has the potential to have a significant effect on the treatment of other neurological conditions in the near future.(33) In addition, the clinical trial design (a randomised controlled trial with a sham control), in a large number of patients for a rare disease, with validated and clinically meaningful outcomes, also represents an innovation which may be emulated for other rare diseases. Overall, the innovative nature of nusinersen for the treatment of this devasting rare disease aligns with the Department of Health's UK Strategy for Rare Diseases to provide patient access to beneficial innovations.(34)	
20	**Consultee (company)**	Biogen Idec Ltd.	Paragraph 3.18 noted the committee's consideration of whether there were any health benefits not captured in the analysis and its conclusion that it was difficult to assess how they might affect the cost-effectiveness estimates. One of the difficulties with capturing the health benefits of nusinersen, aside from those associated with evaluating QoL in infants and children, is determining the most appropriate QoL tool for children with SMA. A recent systematic literature review found that the Paediatric Quality of Life Inventory was the most commonly used tool to measure QoL in children, but there were no disease-specific tools to capture QoL in children with SMA.(17) Therefore, it is highly likely that QoL benefits attributable to nusinersen weren't fully captured with generic tools, specifically given the multiple contexts affected and limited by their disease in relation to peer group, family, classroom and community.(17) Secondly, health benefits were captured from a range of ages in the CHERISH trial using the same instrument; however, the cognitive differences vary substantially between each year in a child's development.(17) Therefore, it is likely that the same QoL tool will capture different health benefits for children aged 2-4 years old than for children aged 8-12 years old. Furthermore, as recognised by Vaidya et al (2018), SMA presents at different ages and subsequently in different types/severity levels which makes it particularly challenging to capture the health benefits within a clinical trial setting. Given the problematic nature of QALYs in this patient group, health benefits need to be viewed in the round, not just as contributing towards the generation of QALYs. While data and methods can be further explored to improve HRQoL and utility estimates (e.g. extending the case vignette study) in order to determine the most appropriate tool for HRQoL data collection within an MAA, it is argued that the QALY is unlikely to capture all the health benefits associated with nusinersen. From this perspective, the QALY may be intrinsically incapable of fully incorporating the benefits of nusinersen into the estimates of cost-effectiveness. In addition, given the rarity of the condition, data quantifying the true cost to the health and social care systems, to carers and to wider society in the form of lost productivity, are sparse.	Thank you for your comment. This section has been removed. However, the difficulties with the use of quality of life tools in people with SMA is discussed in section 3.17 of the FAD which also notes that the committee considered that the utilities may not have captured some health benefits associated with nusinersen. This uncertainty will be addressed in the MAA.
21	**Consultee (company)**	Biogen Idec Ltd.	Paragraph 3.23 noted the committee's assessment that nusinersen for early onset SMA could meet the end-of-life criteria but that, for later onset, it did not. As stated by the committee, blurred boundaries between different types of SMA, the nature of the population and the rarity and severity of SMA, it could be considered unreasonable to apply a different level at which	Thank you for your comment. The committee considered this

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			nusinersen would be considered cost-effective depending on the age of onset of SMA, but a conclusion was not reached on this. Biogen agree with the committee that it may be unreasonable to apply different cost-effectiveness criteria depending on the age of onset of SMA and, considering the 60% share of incident cases of SMA accounted for by infantile onset, would suggest that end-of-life criteria should be applied across the board. Further understanding from NICE is sought on the implications of the end-of-life criteria for the ICER that can be considered.	comment but felt it was not appropriate to apply end of life rules for people with SMA types 2 and 3 as they did not meet end-of-life criteria. However, both early and late onset have now received positive recommendation in the context of a managed access agreement.
22	**Consultee (professional group)**	British Paediatric Neurology association	Nusinersen has clearly demonstrated a very robust therapeutic effect with highly significant positive results on the functional outcome of affected SMA children, their health and survival. Following studies in which the UK centres took part (Lancet 2016, PMID: 27939059; NEJM 2017 PMID: 29091570; NEJM 2018, PMID: 29443664) this drug was approved by FDA in December 2016, less than 4 months from the study end; and by EMA shortly after. Severely affected children with SMA1 (who never acquire sitting position and who typically die at a mean age of 9 months of life) now have the prospect of a therapy that – especially if initiated close to the onset of disease- can substantially reduce the complications we see in this disease, such as respiratory and feeding problems as well as improved motor skills such as sitting in some children and even standing. There is no doubt that Nusinersen is an effective therapeutic intervention for SMA, both from clinical experience as well as from the research publications. It is also clear however that delaying the initiation of treatment in this severe neurodegenerative disease leads to worse outcome. If initiated before 13 weeks of age, the results are very positive.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a managed access agreement. The benefits of nusinersen are summarised in section 3.7 and 3.9 of the FAD. Furthermore, section 3.10 of

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				the FAD now addresses early administration of nusinersen.
23	**Consultee (professional group)**	British Paediatric Neurology association	**Could Nusinersen be more effective in other SMA types?** For conditions like SMA type 3 with a less aggressive progression, a window of opportunity for improvement with treatment may be larger. In this condition approximately 80- 90% of children with SMA type 3, with onset before the age of three years (classified as SMA 3a), will lose the ability to walk by late teens. In a recently presented and publically available long term extension study of 14 children with SMA type 3 originally recruited in the Nusinersen clinical trial (NEJM), the Median (25th, 75th percentiles) distance walked increased over time by 17.0 (0.0, 51.0) meters at Day 253 and 98.0 (62.0, 135.0) meters at Day 1050. These figures therefore indicate a continued improvement on Nusinersen, as also mirrored in the SMA type 1 children.	Thank you for your comment.
24	**Consultee (professional group)**	British Paediatric Neurology association	**Nusinersen treatment for all SMA types?** We are aware, as clinicians, that children with SMA type 1 on Nusinersen are now becoming more able and stronger than our SMA type 2 children not on Nusinersen. This, to the parents, appears as discrimination. Whilst a clinical diagnosis, on whether a child can sit, stand walk denotes their SMA type clinically; 1,2,3 or 4, we are also aware that SMN2 copy numbers can also have a predictive value, and this was used in the clinical trials (SMN2 copy number =2). Whilst some SMA type 1 children generally have 2 copy numbers of SMN2, equally there are SMA type 2 children that also have this number and within the SMA type there is a clinical spectrum; SMA Type 2 can range from a weak type 2 (2.1) to a strong, almost SMA type 3 (2.9) child. Therefore to stipulate copy numbers of SMN2 is not feasible, however clinical judgement and response to a treatment should be taken into account. If a child is improving both motor milestones and respiratory but also time spent out of hospital, this is all beneficial and ultimately cost saving. If treatment with Nusinersen means that an SMA type 2 child behaves more like an SMA type 3 child, this reduces the medical costs and interventions significantly.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a managed access agreement. The committee discussed the use of SMN2 copy number to predict the course of disease but clinical experts considered it to be less reliable than current classification systems (see

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				section 3.5).
25	**Consultee (professional group)**	British Paediatric Neurology association	**High cost treatment; benefits?** We are fully aware that one of the concerns, explicitly expressed by NHSE and NICE relates to the perceived or likely high drug cost of Nusinersen. We completely understand that treatments should be cost effective and the lowest cost possible, weighing up the benefits and other costs incurred. Successful negotiations have been held already in 20 countries where Nusinersen is available to patients affected by early onset SMA (including Scotland), while the drug is anticipated to become available imminently in another 20 countries as a result of a clear path for approval. We support the robust processes to ensure appropriate drugs are funded, however the process on this occasion has been extremely lengthy and there has been no negotiation made with the company re; pricing.	Thank you for your comment. The appraisal process was delayed for several reasons including that the company wished to submit further evidence and because the company have been in discussion with NHS England to negotiate a commercial agreement.
26	**Consultee (professional group)**	British Paediatric Neurology association	The UK is number 1 in its ability to run effective trials and we have engaged with pharma companies to ensure that our children have access to these trials. However given the problems that are encountered by our processes to get drugs funded will have repercussions regarding Pharma's willingness to engage with the UK, in all drug related trials, and therefore this will have a detrimental effect to the degree of funding afforded to departments and the NHS, which will only serve to reduce our abilities to run 1st class clinical trials and be a world leader in this field.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a managed access agreement. The funding of individual clinical departments is

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				not within NICE's remit.
27	**Consultee (professional group)**	British Paediatric Neurology association	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS** Previously the standards of care adopted for care of these patients was purely supportive, however with the development and use of Nusinersen this has changed. The provisional recommendation of not considering Nusinersen would negate this and mean patients would be deprived the chance to gain motor skills rather than loose them and live rather than die. **We would not be in support of this.** In the UK we have collected data on all the children treated with Nusinersen to date and up until now we have not had any deaths, no adverse events and all children have continued to improve or stabilise. This data has been discussed and presented at a national workshop where paediatricians, paediatric neurologists, respiratory physicians and physiotherapists, and intensivists from the entire UK attended. We as clinicians are collecting data and entering this as part of a national database monitoring closely the effectiveness in real-time of these children on the Nusinersen as part of the EAP.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a managed access agreement.
28	**Consultee (patient/carer group)**	Muscular Dystrophy UK	As a charity supporting people being denied treatment for spinal muscular atrophy (SMA), we are extremely disappointed that the committee has rejected nusinersen. This is the first and currently only treatment for people with spinal muscular atrophy, which is a devastating and progressive condition. We appreciate the financial constraints that the NHS has to operate within, however, we also strongly believe that this treatment should be made available to those that would benefit from it, on the basis of clinical decision making, rather than on purely cost-effectiveness grounds. The process of assessing nusinersen in the UK has been lengthy, with over 7 months between European Medicines Agency approval and the start of the NICE appraisal process. It will be at least 18 months since the treatment was approved by the time the NICE process concludes. This is completely unacceptable. During this time, the condition of patients who could benefit from the treatment will have irrevocably altered and it is only because of the Expanded Access Programme that we have not seen many children dying during this period. There is a moral imperative for devastating progressive conditions, like SMA, to be be assessed rapidly. We do not believe that the Single Technology Appraisals route has been an appropriate tool for assessing this treatment and feel it highlights the shortcomings of the existing system in terms of adequately assessing rare disease treatments.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a managed access agreement. The appraisal process was delayed for several reasons including that the

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				company wished to submit further evidence and because the company have been in discussion with NHS England to negotiate a commercial agreement. Following extensive discussion with all stakeholders at scoping, it was decided that this topic should be appraised as an STA.
29	**Consultee (patient/carer group)**	Muscular Dystrophy UK	Nusinersen has been shown to have positive, potentially life-changing and life-saving results, particularly for children with SMA, a point emphasised by clinicians and recognised by the committee. The treatment has been shown to improve longevity but also motor function, including respiratory function. It also represents a bridge to new emerging treatments for people with SMA. Without access, the condition will be left untreated and people's health and independence will progressively decline.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model

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				and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
30	**Consultee (patient/carer group)**	Muscular Dystrophy UK	We are concerned that this recommendation could result in children with SMA Type 1 dying when the current Expanded Access Programme is closed in November 2018. If NICE do not change their decision or find an alternative means of granting access (such as a managed access agreement) then we know that babies diagnosed with SMA Type 1 after November 2018 are unlikely to reach their second birthday. In our eyes, this represents a clear moral imperative for the committee to re-evaluate their current stance.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
31	**Consultee**	Muscular	We do not believe that the provisional recommendation constitutes suitable guidance to be implemented by the NHS. We are	Thank you for

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	(patient/carer group)	Dystrophy UK	concerned that the evidence supplied by patients, carers and clinicians on the physical, emotional and practical benefits of nusinersen do not seem to have been given significant weight in the consideration of the evidence.	your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
32	**Consultee (patient/carer group)**	Muscular Dystrophy UK	We were pleased to see mention of the possibility of a managed access agreement to address the uncertainties in evidence of long-term benefits highlighted by the committee. However, it was concerning to read that the committee felt the details of the company's proposed managed access arrangement were "vague and currently insufficient for it to assess whether it could be an option." Given the impending closure of the Expanded Access Programme, we strongly believe that NICE, NHS England and the company should work together to secure a managed access arrangement for nusinersen as soon as possible and no later than end of October 2018. Evidence has shown that the treatment is clinically effective and is currently the only treatment available for the condition. If the only uncertainties are around cost and data then these can be addressed via an access agreement whilst ensuring patients can continue to benefit from the treatment.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation

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				comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
33	**Consultee (patient/carer group)**	Muscular Dystrophy UK	We understand that the evidence currently available suggests that the technology is particularly useful at the earliest stages suggesting it could be more appropriate to prioritise treatment for children at diagnosis and pre-symptomatic children. This relies on early diagnosis. Symptoms for Type 1 are within the first few months of live and sometimes before birth, whereas symptoms for Type 2 and 3 are usually seen from 7-18 months.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now

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				recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA. Furthermore, section 3.10 of the FAD now addresses early administration of nusinersen.
34	**Consultee (patient/carer group)**	Muscular Dystrophy UK	We strongly believe that “Type” of SMA should not be the determining factor in whether or not a patient receives treatment. There is such a broad spectrum across each type and the boundaries between types can be blurred. For example, some stronger Type 1s currently accessing nusinersen on the Expanded Access Programme are now sitting up - clinically speaking, this would now make them a Type 2.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.

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				Further, the committee highlighted the difficulties with the current classification in section 3.2 of the FAD and notes in section 3.29 that they considered it unreasonable to apply a different level of cost effectiveness for these populations.

35	**Consultees (patient/carer groups)**	Spinal Muscular Atrophy Support UK and The SMA Trust	**Has all the relevant evidence been taken into account?**
			
			NICE's committee papers: evidence of population with SMA
			
			The evidence suggests that the committee's estimation of the population that would access treatment is too high.
			
			We understand NICE is basing its discussions on the following statement in the summary slide 'Disease Background':
			
			'It is estimated that about 100 people are born with SMA per year in the UK, and currently between 1,200 and 2,500 children and adults with SMA in the UK.
			
			We have been unable to ascertain how NICE has derived its prevalence and incidence data.
			We note that NICE's figures are similar to estimates we were aware of in 2013 derived as follows:
			
			• At the 2013 SMARTnet /Patient Registry meeting, a lead clinician stated that **there are some 1200 people affected by SMA in the UK at any one time – children and adults**.
			
			• We asked another leading clinician that same year for their calculation which, based on the then estimated incidence of **100 children born with SMA per year**, they gave as follows
			
			  • **Type I**: accounts for 50-60% of all SMA but median life expectancy is 1 year, so rough estimate is that there are about **25** children alive in the UK with Type I at any one time.
			  • **Type II**: median life expectancy about 25 years, 25% of all SMA so prevalent population is 25 x 25 = **625.**
			  • **Type III**: by the same reasoning 25x70=**1750.**
				Thank you for your comment. The comment acknowledged and considered the comment including that not everyone eligible will be treated with nusinersen.
				
				The potential budget impact of the adoption of a new technology does not determine the Appraisal Committee's decision so the estimates of the population size would not significantly

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			• **TOTAL approx. 2,500,** but this is the upper limit and the **true figure is probably around 1,500-2,000.** As there were no other figures available at this time, these figures and calculations became public. We consider this to be incorrect based on evidence presented in these two recent studies: • Verhaart I *et al.* (2017) **Prevalence, incidence and carrier frequency of 5q–linked spinal muscular atrophy –a literature review.** *Orphanet J Rare Dis* 12: 124. • Verhaart I *et al.* (2017) **A multi-source approach to determine SMA incidence and research ready population.** *J Neruol* 264: 1465-1473 These conclude: I**ncidence**: approximately one in every 10,000 babies worldwide are born with a type of SMA. In England and Wales in 2017, there were 679,106 live births. This suggests that in that year approximately 68 babies were born with a type of 5q SMA. **Prevalence** -between 1 and 2 people in every 100,000 worldwide have a type of SMA. In 2017, the population of England and Wales was approximately 58.4 million. Based on this, it is estimated that between 585 and 1170 people living in England and Wales have SMA. We are aware these papers are based on global observations of incidence and prevalence but until we have an accurate UK wide register of those born with 5q SMA and those living with 5q SMA we ask NICE to use them to guide analysis and decision making. **Population that would seek treatment** From the perspective of NICE's decision making, it is not only important to know the actual population but also to be aware and take into consideration that: • **Not everyone who has 5q SMA will want treatment**. Reasons cited are: o the invasive method of administration and necessary commitment to its long-term repetition o the unknown long-term outcomes o an awareness there are more treatments, such as gene therapy, on the horizon. We remind NICE of our 2018 survey of parents/carers of children and young people with SMA and adults with SMA which we submitted in which: o 18%. of people with SMA (total respondents 56) – most of whom would be adults - said they would not want nusinersen treatment o 5% of parents/carers (total respondents 55) said they would not want nusinersen treatment for the child / young person they care for	impact on the final decision.

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			The same observation applies to both groups in that those not interested in treatment may not have been engaging in the discussion let alone have responded to the survey – in which case the percentage who would not seek treatment may be higher. • **The treatment may not be clinically safe for everyone with SMA** • There has been **no clinical evidence of the treatment for those with SMA Type 0 or 4**. Although the number with these types of SMA are small, again this lowers the likely population that will seek treatment if it is funded by the NHS **In summary: when considering all with 5q SMA, we suggest that an appropriate population base is:** o ***Incidence:* 1 in every 10,000 – approximately 68 babies born with 5q SMA each year in England and Wales.** o ***Prevalence:* between 1 and 2 people in every 100,000 worldwide have a type of SMA - approximating to between 585 and 1170 people living in England and Wales having SMA** **We further suggest that the population that would seek treatment is lower than the prevalent figure:** o **Not everyone who has 5q SMA will want treatment** o **The treatment may not be clinically safe for everyone with SMA** o **There is no clinical evidence of the treatment for those with SMA Type 0 or 4**. **We are concerned that an over estimation of the population who would seek and for whom this treatment would be clinically safe may lead to incorrect assumptions by NICE as to the total budget that would be required**	
36	**Consultees (patient/carer groups)**	Spinal Muscular Atrophy Support UK and The SMA Trust	**Has all the relevant evidence been taken into account?** **Consultation Paper 3.5 NICE's Clinical Evidence** We note that NICE only discusses evidence from the published results of the clinical trials ENDEAR and CHERISH. We understand that Biogen will be submitting further evidence published in 2018. We would like to be assured that NICE has considered the additional recently published clinical evidence from 'real world' studies. Though the studies were not all conducted in the UK, all the clinical practice is guided by the 2017 internationally agreed Standards of Care for SMA (**Mercuri, E *et al.*** (2017) **Diagnosis and management of spinal muscular atrophy: Part 1: recommendations for diagnosis, rehabilitation, orthopedic and nutritional care.** Neuromuscul Disord. 2018 Feb;28(2):103-115. and **Finkel, R et al** (2017), **Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics**. Neuromuscul Disord. 2018 Mar;28(3):197-207.) We note that the real-world studies only review outcomes for children with SMA Type 1 for the first six months of treatment but consider 'real world' evidence critical to decision making. They all assist with confirming the certainty of evidence of effectiveness (see below). In particular we refer to: **Reviews of the Expanded Access Programme:** • **Europe -** 33 children aged from 8.3 to 113.1 months - December 2016 - May 2017. **Aragon-Gawinska, K *et al*.** (2018) **Nusinersen in spinal muscular atrophy type 1 patients older than 7 months. A cohort study** Neurology® 2018;00:1-7. doi:10.1212/WNL.0000000000006281	Thank you for your comment. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic

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			• **Australia** – 16 patients aged 2.5 months to 35.7 years November 2016 – September 2017 **Farrar, M *et al.*** (2018) **Nusinersen for SMA: expanded access programme** J Neurol Neurosurg Psychiatry 2018;**89**:937–942. doi:10.1136/jnnp-2017-317412 • **England - Great Ormond Street Hospital** – 21 patients aged 8.3 – 113.1 months March – October 2017 **Tillmann, A *et al.*** (2018) **Spinal Muscular Atrophy (SMA) type 1, a changing phenotype: Implications for motor function and physiotherapy management from the Nusinersen Expanded Access Program (EAP)** APCP Journal Volume 9 Number 1 • **Germany** – 61 patients aged 1 – 93 months in seven neuromuscular centres November 2016 – June 2017 **Pechmann, A *et al.*** (2018) **Evaluation of Children with SMA Type 1 Under Treatment with Nusinersen within the Expanded Access Program in Germany** Journal of Neuromuscular Diseases 5 (2018) 135-143 DOI 10.3233/JND-180315 • **Italy** – 104 patients – aged 3 months – 19 years 9 months - first six months of EAP **Pane, M *et al.*** (2018) **Nusinersen in type 1 SMA infants, children and young adults: Preliminary results on motor function** Neuromuscular Disorders 28 (2018) 582-585 30 May 2018 Also: • **Hoy, S** (2018) **Nusinersen: A Review in 5q Spinal Muscular Atrophy** CNS Drugs (2018) 32:689-696 Published online 20 July 2018 © Springer Nature Switzerland AG 2018 **In summary we ask NICE to include in their evidence base the outcomes of 5 'real world' studies of 235 patients age range 1 month – 35.7 years receiving treatment via the global SMA Type 1 Expanded Access Programme.**	and types 1, 2, and 3 SMA in the context of a MAA.
37	**Consultees (patient/carer groups)**	Spinal Muscular Atrophy Support UK and The SMA Trust	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** **Consultation Paper 3.6 NICE's conclusion re: clinical effectiveness in terms of survival and improved motor function.** We note **Hoy's overview** (cited above) which supports NICE's conclusion. 'Results from an expanded access programme support the efficacy of nusinersen in the real-world setting.'	Thank you for your comment.
38	**Consultees (patient/carer groups)**	Spinal Muscular Atrophy Support UK and The SMA Trust	**Is the summary of clinical effectiveness a reasonable interpretation of the evidence?** **Consultation Paper 3.7. NICE's discussion of other health benefits for early onset SMA**. This focuses on discussion of outcome measures used in the trials. It acknowledges the patient experts view of these 'other' valuable benefits and the importance of any stabilisation and even small improvements in symptoms, especially improvements in motor function. **Aragon-Gawinska, K *et al.*** confirm this and describes parental reports of the wider impacts, impacts that are significant for quality of life: 'It should be noted that many parents reported improvements during treatment with nusinersen that were not captured by the	Thank you for your comment. Section 3.7 (now 3.8) of the FAD notes that patient experts considered the benefits of nusinersen from

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			measures used and that were not predefined in data collection such as louder voice, better endurance, and more efficient coughing. Better definition of these outcomes might be useful for long-term follow-up of these patients.' **Pechmann, A *et al.*** also note in their study, 'Further research is needed to evaluate the impact of changes in CHOP INTEND score on daily life and on quality of life in children with SMA type 1, which are not as obvious as changes in motor milestones.' **Aragon-Gawinska, K *et a*l.** confirm NICE's conclusions when they state: 'Our results are in line with the phase 3 study for nusinersen in patients with SMA1 treated before 7 months of age and indicate that patients benefit from nusinersen even at a later stage of the disease.' And 'Despite its limitations, this study provides Class IV evidence that nusinersen is beneficial for patients with SMA1 between 7 and 113 months of age.' ENDEAR's respiratory function, time on ventilator and hospitalisations evidence is currently in confidence and therefore not discussed in NICE's conclusions. With regard to this, though not 'clinical evidence' and already submitted, we remind the committee of the results of our own survey in the UK when we heard from 29 parents whose children had received nusinersen treatment, many of whom had had this for longer than six months: • **Numbers:** Type 1 - 19; Type 1 / 2 - 9; Type 2 - 2; Type 3 – 1. • **Age range:** <7 months – 9+ years. • **Treatment duration**: 0-4 injections – 8; 5-7 injections – 18; 11+ injections -1). The % reports from 20 parents giving open comments of their observed outcomes of their treated child was as follows: • Physical / muscle improvements 95% • Much happier 40% • Respiratory gains 35% • General improvement in health 20% • Increased vocalisation 10% Typical quotes, taken from the qualitative part of our study, that **highlight the impact of the motor milestones on daily living** are: 'Practically she is able to perform more tasks herself and gained strength to use her own wheelchair.' **Type1, treatment started age 13 - 24 months, 5-7 injections**	both trials and in practice were valuable to patients and their families. This section was amended according to the updated information (no longer academic in confidence) presented by the company. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.

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			Typical quotes that **highlight the gains are not just with mobility and suggest an impact on respiratory function** are: 'He has been managing colds all through winter at home whereas before he was in intensive care on life support for every cold he got. He is a happy boy who can now start to explore his surroundings, he is also beginning to talk and can say Mum and dad and can sing and clap.' **Type 1, treatment started < 7 months, 5-7 injections** 'My child required/relied on bipap before treatment and her lungs were getting worse and worse. ….However, nusinersen has stabilised / improved her breathing. She now only requires bipap for sleep and her settings have been turned down following sleep studies.' **Type 1 treatment started 13-24 months, 5-7 injections** 'He can tolerate sitting up for hours without any respiratory support…..Respiratory wise he has gone from being ventilated 22 hours a day to 16 hours a day.' **Type 1, treatment started <7months, 11+ injections** 'Her biggest joy is being able to cough better, and deal with mucus plugs without so much chest physio and cough assist. Also, previously every illness (respiratory or gastric) meant non-reversible deterioration, and now she bounces back almost to the same level as before the illness.' **Type 1 / 2, treatment started 37 months +, 5-7 injections** **In summary: we are pleased to see NICE recognising that any improvements would be highly valued by patients and that it provides important health benefits for early-onset SMA. We suggest that real world studies that comment on parent views and our own survey indicate less uncertainty than NICE concludes.**	
39	**Consultees (patient/carer groups)**	Spinal Muscular Atrophy Support UK and The SMA Trust	**Is the summary of clinical effectiveness a reasonable interpretation of the evidence?** **Consultation Paper 3.8 Nusinersen substantially improves motor function for people with later-onset SMA** We note and agree with this conclusion. The real-world studies (see 2) of patients with SMA Type 1 aged I month to 35.7 years indicate, as summarised by **Pechmann, A *et a.l*** that, 'Although this study does not provide evidence comparable to a randomized controlled trial, the results indicate that even in advance stages of the disease, nusinersen can lead to improvement of motor function as measured by CHOP INTEND'. Given these real-world studies have necessarily been restricted to delivery to those with SMA Type 1 the most severe form of SMA, it may not be unreasonable to suggest, as shown in CHERISH that these findings will be at the very least replicated with SMA Type 2 and 3 with all the very positive implications of such outcomes. We also remind NICE that this conclusion was confirmed in our submission which drew attention to the very positive outcomes of treatment, not just in terms of motor function, for **a teenager with SMA Type 3** and the impact that the gains have had on all aspect of his daily living. We understand his treatment has continued and this parent will be giving NICE a further update on progress.	Thank you for your comment. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic

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				and types 1, 2, and 3 SMA in the context of a MAA.
40	**Consultees (patient/carer groups)**	Spinal Muscular Atrophy Support UK and The SMA Trust	**Is the summary of cost effectiveness a reasonable interpretation of the evidence?** **Consultation Paper 3.10 Transition probabilities based on assessment of motor milestones** We agree with the Evidence Review Group (ERG) comments that the model structure fails to take account of other key factors affecting health-related quality of life such as; participating in activities, respiratory function, pain and physical impairment. We note that the committee concluded that the models had limitations but were nevertheless suitable for decision making as they were consistent with the main outcomes of the clinical trials. We are not confident that we agree with this conclusion because it is questionable whether the main outcomes were an adequate reflection of the effectiveness of treatment. In **Ethical Challenges Confronted When Providing Nusinersen Treatment for Spinal Muscular Atrophy** Journal of American Medical Association Feb 2018 Volume 172 Number 2**, Burgart, A.M *et al.*** comment on the motor milestone measurements used in the trials as follows: 'Maintaining the most marginal function may be the key quality of life indicator for a patient seeking nusinersen treatment. The measurements used during the trials, while sufficient for patients who met study criteria, may not be sensitive enough to detect minute differences in strength maintained or gained.' Additionally, as shown above (see 4), the range of outcomes measured was limited and did not adequately show their breadth.	Thank you for your comment. Section 3.10 of the FAD (now section 3.13) has changed following the company's amendments to the model. Generic quality of life scores estimate the global QoL and typically capture improvements in specific benefits to individual patients. However, the committee were concerned about benefits not captured in the model (see section 3.17).
41	**Consultees (patient/carer groups)**	Spinal Muscular Atrophy Support UK and The SMA Trust	**Is the summary of cost effectiveness a reasonable interpretation of the evidence?** **Consultation Paper 3.13 Utility values in the economic model are highly uncertain** We agree with NICE's concerns that identifying robust utility values in babies and young children is exceptionally challenging and draw attention to the flaws the measures present as summarised by **Griebsch, I *et al*. Quality-Adjusted Life-Years Lack Quality in Pediatric Care: A Critical Review of Published Cost-Utility Studies in Child Health** Pediatrics May 2005, VOLUME 115 / ISSUE 5 summarises the issues that this measurement brings: • Children undergo dramatic changes in growth and function (e.g., mobility, self-care) at different rates, difficulties may arise to attribute improvements to health care interventions rather than to normal development. There is no methodologic guidance about how this should or even might be dealt with. • All current generic measures (with the exception of the Health Utility Index Mark 2) are derived from adult populations, and additional attributes that are particularly relevant to child health, including, for example, autonomy, body image, cognitive	Thank you for your comment. The company's approach has changed in the most recent iteration of the model. Consequently, the conclusion in section 3.13 of the FAD (now

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			skills, and family relationships, may not be captured by these measures. Furthermore, no generic instrument for children and infants **younger than 5 years** is available. • Children, particularly young children do not have the cognitive ability to comprehend and complete valuation or even measurement tasks. The implication is that, for very young children, some form of proxy inevitably will be used for measurement tasks, whether this be the clinician or the parent. Although parents may be perceived by economists as the more appropriate source of measurement and/or valuation, the potential for interaction between the utility function of the parent and the proxy (their child) for whom he or she is making the measurement/valuation may lead researchers to choose to use clinician judgment to avoid this problem. The issues with this are that: clinicians only see and record a 'snapshot' which may not truly represent the changes taking place and impact on daily living for both child and parents; measurement tools are insufficiently subtle and limited in their measurements. This last point is confirmed by the above comments (see 4) and the many studies that show this, for example, **Srikrishna S, *et al.*(**2009*)* **Is there a discrepancy between patient and physician quality of life assessment?** Neurourol Urodyn. 2009;28(3):179-82. doi: 10.1002/nau.20634. **In summary: we agree that both the company and the ERG approaches had serious limitations. We understand NICE's decision to use both approaches sought to address this, but are concerned that the final values may not appropriately reflect the impact of the worst health states caused by untreated SMA as reported in clinical and patient expert evidence.**	section 3.17) has been amended and reflects that the committee did not consider that the utility values have captured all benefits. This uncertainty will be addressed in the MAA.
42	**Consultees (patient/carer groups)**	Spinal Muscular Atrophy Support UK and The SMA Trust	**Is the summary of cost effectiveness a reasonable interpretation of the evidence?** **Consultation Paper 3.14 Carer disutilities** We note NICE concluded that quantifying carer -related disutilities was extremely difficult and that the committee was concerned that the proposed model resulted in the counter-intuitive outcome whereby, 'the largest carer disutility was seen in the best health state. We agree with this concern and remind NICE of our survey in which 56 people with SMA, 55 parents/carers and 21 relatives described the huge 'carer burden' of the untreated condition on their lives. In contrast, in 'open comments', 20 families with children still at early stages of treatment described the beginning of the reduction of this 'burden' in the following ways: • Given hope 65% • Emotionally positive and happier 40% • Decreased care needs 20% One family summarised the pre and post treatment change in 'burden' as follows: 'When your child is unstable and having frequent hospital / ambulance admissions this is very draining both physically and emotionally on the whole family. We are more relaxed and able to enjoy day to day life and activities so much more now. SMA is very tough on you as a carer / sibling, but with his stability and health being so much better we feel a lot more happy as a family.' **Type 1, treatment started <7months, 11+ injections**	Thank you for your comment. Please note that as the company's approach changed in the most recent iteration of the model, section 3.14 of the FAD (now section 3.18) has been amended. Further, the committee have taken into account the consultation comments including the views of patients, carers and

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				clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
43	**Consultees (patient/carer groups)**	Spinal Muscular Atrophy Support UK and The SMA Trust	**Is the summary of cost effectiveness a reasonable interpretation of the evidence?** **Consultation Paper 3.15 The ICER is uncertain** **Consultation Paper 3.18 Uncaptured health benefits** We agree with NICE that there is uncertainty and acknowledge the committee's efforts to address flaws in the models in its conclusions. We note that the paper states 'It was not presented with any data to show other distinct and substantial benefits of nusinersen that have not been captured in the economic analysis. We acknowledge that our submission data was qualitative and anecdotal, but it was directly from members of the UK SMA community. We therefore seek an assurance that the economic analysis covered all direct health and personal health and social services costs and reflect the observations submitted in our survey results, namely: • **mental health:** o 56% of 132 of 'untreated' respondents reported the person with SMA did not have enough support and intervention to keep emotionally well o 54% of 132 of 'untreated' respondents reported the person with SMA did not have enough support and intervention to get enough sleep o 67% of 132 of 'untreated' respondents reported the main carer did not have enough support and intervention to keep emotionally well o 73% of 132 of 'untreated' respondents reported the main carer did not have enough support and intervention to get enough sleep • **equipment costs and housing adaptations**: o our survey detailed the huge range required • **emergency hospital stays, surgery and clinic time:** o again, these events and related costs are enormous • **continuing health care (CHC) cost:** o these can be significant and, combined with social care / personal budget, up to 24 hour	Thank you for your comment. The company's approach to capturing costs changed in the most recent iteration of the model in response to many consultation comments about cost (see section 3.19 of the FAD). Please note that the cost data reported in the comment was provided to the company. Section 3.19 highlights the uncertainty in the costs. The committee have taken into

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			Though we accept there is uncertainty as to future long-term outcomes for those treated with nusinersen, the evidence to date clearly indicates that these wider costs will potentially reduce significantly. We would like assurance that this potential is adequately reflected in the ICER. We also seek assurance that the model reflected that the health impact is not on **one** carer but on many e.g. grandparents who also often play a key role. Also that due to the 'carer burden' of caring for someone with SMA, that it impacts on other caring responsibilities of the carer. In our survey: • 32% of 128 respondents reported the carer had caring responsibilities for **ageing parents** – with the potential that they would not be able to give those parents the care they will need and that these costs will therefore fall to health and social services • 51% had caring responsibilities for **other children** with some reporting that their focus on the child with SMA and their needs was impacting negatively on siblings' mental health and behaviour with potential health related costs We are concerned that however much effort NICE has made to adjust the ICER's to better reflect the evidence presented and address shortcomings that do not reflect 'real-world patient expert reports, the appraisal system remains fundamentally flawed. From our perspective there needs to be a much more holistic inter-departmental approach to assessing the costs and benefits of treatment. Only then can the ICERs really begin to reflect the true potential value of this treatment. As examples of this, SMA impacts on: • **education costs**: requiring Teaching Assistants, school adaptations, University PAs • **work costs:** carers (parents and grandparents) and patient – loss of potential productivity and contribution to the economy through work / taxes. In our survey: o 52% of 132 respondents reported that the interventions and support they have is not enough for the person with SMA to work / study for the hours they wish o 70% of 132 respondents reported they were not enough for the carer to work / study for the hours they wish • **health and social care costs borne by families:** o 45% of 132 respondents reported that the interventions and support the person with SMA and their carers have are not enough for that person to manage financially o 60% of 132 respondents reported that they are not enough for the carer to manage financially • **equipment and housing adaptation costs borne by families:** Examples from our survey of items that many respondents reported were not NHS funded: o 71% of those using a wizzybug o 70% of those needing a specialist car seat o 57% of those needing a wheelchair accessible vehicle o 52% of those who had needed home adaptations o 50% of those needing a powered wheelchair o 50% of those requiring assistive technology **SMA is a progressive condition which mean these costs increase over time. Treatment that results in stability alone can result in a huge reduction in these costs.** **In summary: we seek an assurance that the economic analysis covered all the real-world costs of all the health and personal health and social services required to support a person with SMA and their family and**	account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA (see section 3.12 of the FAD). The text in section 3.2 (now section 3.3) of the FAD has been amended to reflect that multiple carers are affected. The company's updated economic model assumes more than one carer is affected (see Section 3.18 of the FAD). However, section 3.18 highlights the high levels of uncertainty in the estimation of carer utility. The uncertainties will be addressed in the MAA. NICE regularly

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			included the impact of SMA affecting more than one carer. We also wish it to be noted that we consider the model falls short in that it fails to cover the real-world costs that lie outside the realm of health and social services. We are aware this is not possible within this appraisal but consider that this needs to be urgently addressed by NICE.	reviews its methods.
44	**Consultees (patient/carer groups)**	Spinal Muscular Atrophy Support UK and The SMA Trust	**Are the provisional recommendations a sound and suitable basis for guidance to the NHS?** **Consultation paper 3.16.** states 'Although the committee recognised that a managed access arrangement could reduce the risk to the NHS, the ICER for nusinersen would need **to plausibly be within a range that could be considered cost effective**, and it would require NHS England, patients, carers and clinicians to sign up to it. **Due to nusinersen having been assessed via a Single Technology Appraisal (STA), we consider the ICER threshold is inappropriate and urge flexibility when establishing what will be an appropriate range.**	Thank you for your comment. The company's economic model has changed. The ICERs presented for later onset were considered plausibly cost-effective (see section 3.21 and 3.3.1 of the FAD). The committee considered this alongside the consultation comments received, and the updated MAA proposal, including an improved commercial proposal (see section 3.3.1). The recommendations in the FAD have now changed. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the

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				context of a managed access agreement (MAA).
45	**Consultees (patient/carer groups)**	Spinal Muscular Atrophy Support UK and The SMA Trust	**Are the provisional recommendations a sound and suitable basis for guidance to the NHS?** **Consultation Paper 3.20** We note NICE's statement that its decision to appraise the treatment via an STA rather than via a Highly Specialised Technology (HST) was 'because the population covered by the marketing authorisation is larger than that which can be considered in HST evaluations'. We refer back to our previous comments (See 1) highlighting our concern about the figures used by NICE to draw this conclusion. We also wish to draw attention to the thresholds comparable regulatory bodies use for considering rare orphan / ultra orphan medicines: • **Scotland** is introducing a new definition of 'ultra-orphan medicines' that can treat very rare conditions affecting fewer than 1 in 50,000 people - around 100 people or less in Scotland. This will include SMA and allows the Scottish Medicines Consortium (SMC) the ability to treat some medicines for rare orphan diseases as ultra-orphan medicines. www.news.gov.scot/news/treatments-for-rare-conditions • **The European Medicines Agency** states that for orphan designation, the **prevalence** of the condition in the EU must not be more than 5 in 10,000 (1 in 2,000) or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development; Though it is not clear what population threshold NICE uses given its HST guidance (August 2018) now states that for a topic to be selected, 'the target patient group for the technology in its licensed indication' has to be 'so small that treatment will usually be concentrated in very few centres in the NHS' we understand that previously **NICE's commonly accepted threshold** for considering scoping a treatment as an HST was, that it would be accessed by fewer than 500 patients in England and Wales. If this were the case this would be the equivalent of **1 in 110,000 (Population for England and Wales 2017).** If the threshold moved in line with Scotland it would in contrast, include **1,313 patients.** As outlined in (1) above, the total target population would come well within this. We also note that the treatment was excluded from being appraised via an HST because it is 'not commissioned through a highly specialised service.' We question how appropriate such a barrier to HST appraisal is for a condition such as SMA which is clearly rare but for which, for safe and efficient delivery, treatment needs to be delivered as close to a person's home as possible. We note that Biogen's EAP, which has given the drug free has been opened in both highly specialised and specialised centres in response to strong advocacy from patient groups and clinicians which highlighted: ○ A need to circumvent a postcode lottery ○ The need for children not to travel (health risks, burden on families) ○ The capacity issues of centres that were open.	Thank you for your comment. The consultee is referring to comment 35 – please see response to that comment above. Following extensive discussion at scoping, it was agreed that this topic is appropriate for consideration as an STA. The criteria for a topic to be appraised within the HST programme is more broad than just the population size (see item 28 in NICE's Interim process and methods of the HST Programme). However, please note that the recommendations in the Final Appraisal Document (FAD)

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			In view of this, we consider this range of centres is an appropriate response to the treatment needs of this population. It is a credit to Biogen that they agreed to provide the drug to a wide number of centres and that as a result, more than 80 children are having treatment in across the UK. In so doing we imagine Biogen was aware that this very move would offer one more reason to push the drug out of the HST appraisal route into that of an STA for common diseases. We understand that this treatment did not meet 4/7 of the HST topic selection criteria (Sir David Haslam letter to clinicians 3 September 2018). As such it has missed out on being assessed against the higher HST ICER threshold and has instead been assessed as an STA for common diseases. We strongly contest that this is an inappropriate threshold and that the choice of only these two routes has created undue delays and difficulties with the assessment of this treatment and condition. This has meant that, despite the clinical evidence available, there has been no access for anyone other than those with Type 1 < 7 months of age. In contrast, in July 2018 Biogen reported 20 European countries had access to nusinersen via routine reimbursement. We have provided information and emotional support to one family already who has chosen to move to one of these countries as they are desperate to access treatment. This is not a choice they wanted to make and has been a hugely complex and distressing decision. We know of other vulnerable families also feeling forced to consider this. This is only going to get worse with the imminent closure of the EAP for Type 1 on 1st November. If not resolved before then we will see infants with SMA Type 1 missing the critical early treatment window which gives the best opportunity for positive outcomes and the very real prospect of these infants dying. **In summary: We urge NICE to:** • **Take account of the STA presenting what we regard as an inappropriately low ICER threshold for this treatment and reflect this in a more flexible approach to an agreed higher price threshold within a timely Managed Access Agreement (MAA).** • **Ensure that England and Wales offer access in line with Europe**	have changed. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a managed access agreement (MAA).
46	**Consultees (patient/carer groups)**	Spinal Muscular Atrophy Support UK and The SMA Trust	**Are the provisional recommendations a sound and suitable basis for guidance to the NHS?** **Consultation Paper 3.23** We agree with the committee that 'it could be unreasonable to apply a different level at which nusinersen would be considered cost effective depending on age of onset of SMA'	Thank you for your comment.
47	**Consultees (patient/carer groups)**	Spinal Muscular Atrophy Support UK and The SMA Trust	**Are the provisional recommendations a sound and suitable basis for guidance to the NHS?** **Consultation Paper 3.24** We acknowledge the committee's comment, 'The very high cost of nusinersen means that there is a significant financial risk to the NHS if the committee were to recommend a technology for routine that may not be cost effective' However we point out that many families have expressed that they see this treatment as a vital bridge to further new treatments which are coming close to completion of clinical trials and, one imagines possible applications for licences (**AveXis' AVXS-101, Roche's RG7916 / risdiplam**). In the light of this, we ask the committee to consider that this risk may not be very long term. We were also pleased to read the committee is, 'Willing to be flexible around uncertainty, particularly if access could be managed such that risk to the NHS was reduced' and consider it possible, via a Managed Access Agreement, to collect data	Thank you for your comment. The committee have taken into account the consultation comments including the views of patients,

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			that will reduce uncertainty. We suggest collection of the data could include reviewing and incorporating the work of **Chad Heatwole, MD,** at the University of Rochester, who, in his project, " Development of a Clinically Relevant Outcome Measure for Pediatric SMA Therapeutic Trials." is working to develop SMA-specific patient reported outcome measures for use in SMA clinical trials and clinics. One such instrument, the Spinal Muscular Atrophy Health Index (SMA-HI), was developed and validated using FDA guidelines for SMA patients age 8 to 85. This instrument is currently being utilized to measure therapeutic response in clinical trials. The new work will look at developing properly validated, disease-specific, observer-reported outcome measure for infants and children (under 8 years of age) with SMA.	carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
48	**Consultees (patient/carer groups)**	Spinal Muscular Atrophy Support UK and The SMA Trust	**May the preliminary recommendations need changing because they could have an adverse impact on people with a particular disability or disabilities?** We would argue 'yes', most definitely this decision has an adverse impact on all with SMA who would have wanted and for whom it would have been clinically safe to access the treatment. This decision deprives these people of the possibility of accessing a life-changing treatment that has the potential to have a huge impact on both their quality of life and the quality of life of their families.	Thank you for your comment. As noted above, the recommendations in the Final Appraisal Document (FAD) have changed. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
49	**Consultees (patient/carer groups)**	Spinal Muscular Atrophy Support UK and The SMA Trust	**Is there a clinically distinct subgroup of people in whom nusinersen is expected to be more clinically effective? How could this group be identified in clinical practice?** We note that the cost of the drug is covered by Biogen's EAP for all those currently living with SMA Type 1 (prevalent population). We assume that NHS England's 9 March 2018 commitment to cover the costs of administration of the drug remains in place. We note that there is no clinical evidence for treatment of those with SMA Type 0 and Type 4 We suggest that there are **three groups** all of whom are **of equal importance** and for all of whom there is potential for clinical effectiveness. They are differentiated only so that different 'work streams' can be established within any MAA: **Group A** Clinical evidence (ENDEAR and CHERISH Trials) and 'real-world' studies cited above indicate that early treatment provides	Thank you for your comment. The responses to NICE's specific questions on clinically distinct subgroups was discussed at a workshop facilitated by

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			greater effect. This includes those with Type 1, 2 and 3 where it is clinically safe, and the clinicians and family agree on treatment. Note that, for a range of (personal) reasons, not all will want treatment. For example, **Farrar, M *et al.*** cite, that 4 of 20 families with children eligible for treatment chose not to go ahead. It is a very individual decision requiring informed consent. • **How could this group be identified in clinical practice?** We suggest this group could be easily identified at the time of diagnosis and that for England in any one year, given the incidence (see references and calculations in 1) is likely to be **68 children** including those diagnosed with: • Type 1: 60% - 41 infants age < 6 months • Type 2: 21% - 14 children ages 6 – 18 months • Type 3: 19% - 13 children including o Type 3a ages 18months – 3 years o Type 3b age 3 years plus Though outside the scope of this appraisal, we note and agree with the comments made by **Farrar, M *et al*.** (2018) **Nusinersen for SMA: expanded access programme** J Neurol Neurosurg Psychiatry 2018;**89**:937–942. doi:10.1136/jnnp-2017-317412 'that further education of healthcare professionals seeing infants at risk of SMA type 1 is necessary.' And that 'Newborn screening (NBS) presents as the best opportunity to considerably reduce medical morbidity resulting from a delayed diagnosis of SMA type 1' and indeed the impact of other types of SMA. We note that the UK national screening consultation for SMA is currently calling for comment as to whether criteria for this to be recommended have now been met. One of these is that a viable treatment is available. This relies on a positive recommendation by NICE, at which point there could be the potential for even earlier treatment for these 68 infants each year. We are aware that there are sensitive considerations around the ethics of screening for a condition when the potential impact varies greatly, and the treatment delivery is invasive and requires a long-term commitment but understand that the screening consultation will be addressing potential issues. We note that several US states have recently introduced newborn screening and those with between 1 and 3 *SMN2* copies are offered treatment. However, we note from the internationally agreed Standards of Care the variance between the 'usual' number of *SMN2* copy numbers compared with the possible 'range' (**Tillmann, A *et al.***): • Type 2 have a 'usual' *SMN2* copy number of 2 but a 'range' of 2-4 copies • Type 3a have a 'usual' *SMN2* copy number of 3 but a 'range' of 3 – 5 copies • Type 3b have a 'usual' *SMN2* copy number of 4 but a 'range' of 3 – 5 copies As stated in the International Standards of Care, at the individual level, perfectly accurate predictions cannot be made about the type or severity of SMA based on the *SMN2* copy number alone. This is likely to be because other genetic and possibly environmental factors have an influence on the disease. Added to this there can be delays in obtaining *SMN2* copy number results which, for this group may impact on what is a critical window for intervention. **Group B** We note Biogen's clinical results (CHERISH Trial) and now the SHINE study. We also note the real world studies of those with SMA Type 1including recent publication of the study by **Aragon-Gawinska, K *et al.*** which commented, 'new motor acquisitions were attained even in 8-year-old patients' and **Pane, M *et al*.** whose treatment of those with SMA Type 1 included people in the	NICE. The workshop provided the company with the opportunity to discuss these issues with clinical and patient experts prior to their submission following consultation.

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			age range 3 months to 19 years, 9 months with 95 of the 104 older than 7 months, 'Our results suggest that some therapeutic efficacy is possible even after the first seven months even if the consistency or the magnitude of response was variable and often smaller than those observed with early intervention.' This returns us to the point that stability alone can make a significant difference to quality of life and reducing the true costs of the condition for the individual, their families and caregivers and health and social services (see 9 above). We therefore consider that access is **of equal importance** for all with Type 2 and 3 where it is clinically safe, who are at a **critical point** and the medical team and family/adult agree treatment offers a potential benefit. The need for treatment access for this group is discussed in **Burgart, A *et al's*** article which gives examples of: 'older patients with advanced SMA may be clinically stable in terms of vital physiological functions but on the verge of losing a key functional ability, such as communicating by computer or operating adaptive equipment'. Achieving stability is critical Other examples might be a child whose scoliosis is progressing significantly or, as there is a tendency for children to become weaker at times of major growth spurts such as puberty, children who are reaching this stage. An outcome that maintains stability would be sufficient reason to continue treatment. Not all in this group will want treatment. It is a very individual decision requiring informed consent. • **How could this group be identified in clinical practice?** There would perhaps need to be agreement by a clinical / patient group as to guidelines for what constitutes a 'critical point' and perhaps an overarching national 'appeals group' to ensure equity. If used, as **Burgart, A *et al.*** point out, this would need to 'incorporate appropriate stakeholders, including patient advocates, clinicians, community members, ethicists, and others' We suggest, that though we are aware this is a workload for already pressured clinicians, immediate work is undertaken by a group such as the NorthStar network group and also by clinicians who care for adults with SMA Type 2 and 3. This would be to review caseloads and prepare very brief details of anyone with SMA Type 2 or 3 whom they consider would meet agreed 'critical point criteria' so that numbers and geographical location can be ascertained. If helpful, SMA Support UK could endeavour to assist with identification of this group by contacting the community as we did when we worked with NHS England to trying to establish how many families with children with SMA Type 1 wanted access to the EAP. The UK SMA Patient Registry would be another potential source of assistance – with all working together. Without this preliminary work being undertaken as a matter of urgency, we cannot know the size of this group. **Group C** This group, **of equal importance,** is all those with Type 2 and 3 who are not at a critical point, where it is clinically safe, and the medical team and family/adult agree that treatment has potential to bring stability. We note again the findings of CHERISH and now SHINE and real-world studies that have included older patients with SMA Type 1 to positive effect. Treatment of this group will potentially bring benefits in delaying or preventing individuals reaching the 'critical' point of Group B. These benefits would impact positively on both quality of life and the true costs of the condition for the individual, their families and caregivers and health and social services (see previous points) • **How could this group be identified in clinical practice?**	

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			We suggest a similar exercise to the above. SMA Support UK could help gather this information as could the UK SMA Patient Registry – with all working together. Again, not everyone will want this treatment. It is a very individual decision requiring informed consent. There are adults and young people who won't want this treatment and would rather wait for one with a less invasive delivery. **In summary we identify three clinical sub groups all of whom can be identified in clinical practice. They are all of equal importance as clinical evidence demonstrates they all have the potential of benefiting from treatment. They are differentiated only so that different 'work streams' can be established within any MAA. They are:** • **Group A: all newly diagnosed with SMA Type 1, 2 or 3** • **Group B: all with Type 2 or 3 who are at a 'critical point' in terms of the progressions of their SMA** • **Group C: all with Type 2 and 3 who are not at a critical point but where treatment will potentially bring stability**	
50	**Consultees (patient/carer groups)**	Spinal Muscular Atrophy Support UK and The SMA Trust	**Is there a clinically distinct subgroup of people in whom nusinersen is expected to be more clinically effective? How could this group be identified in clinical practice?** **The logistical challenges of providing treatment** We are very aware that Centres are limited as to how many people they can manage to treat and, as noted by **Burgart, A *et al.***, the need for, 'high-level operational planning and coordination.' Their further comments about the need for different workstreams to meet needs could fit well with our suggested groupings: 'The task of administering the medication consists of at least 3 clinical work flows: the first involves patients for whom lumbar puncture administration is relatively straightforward and can be performed in an outpatient clinic visit, the second involves patients who require a higher level of supportive care to safely undergo the procedure and fully recover to return home, and the third involves patients who are already hospitalized or those whose clinical condition requires recovery in the hospital. These workflows do not necessarily compete with each other for resources, so that patients queued in one work flow are not necessarily ahead of or behind patients queued in another workflow'. **In summary: The EAP has ensured that many paediatric centres are ready and delivering treatment. We don't know how ready adult services are to respond to new work streams. Any exercise to collate numbers for treatment must map out location of patients and a plan for ensuring efficient delivery and geographical equity.**	Thank you for your comment. Please see response to comment 49 above.
51	**Consultees (patient/carer groups)**	Spinal Muscular Atrophy Support UK and The SMA Trust	**Is there a clinically distinct subgroup of people in whom nusinersen is expected to be more clinically effective? How could this group be identified in clinical practice?** **Including all, and allowing for new developments with delivery methods** We note the many developments in delivery for those with spinal scoliosis / who have had spinal surgery as follows: • **Germany** – 26 patients **Mousa, M *et al.*** (2018) **A comprehensive institutional overview of intrathecal nusinersen injections for spinal muscular atrophy** # Springer-Verlag GmbH Germany, Springer Nature July 2018 'Although we achieved 100% technical success in intrathecal nusinersen administration, our practices evolved during the course of this study. As a result of our early experience we developed an algorithm to assist in promoting safe and effective nusinersen administration in children with spinal muscular atrophy regardless of SMA type, abnormal spinal anatomy and complex spinal instrumentation.'	Thank you for your comment. Please see response to comment 49 above. Furthermore, please note that NICE cannot recommend administration for which the committee has not seen any

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			• **USA** – 3 patients ages 12 – 17 years **Veerapandiyan, A *et al.*** (2018) **Cervical puncture to deliver nusinersen in patients with spinal muscular atrophy** Neurology® 2018;91:e620-e624. 'Cervical puncture is a feasible alternative delivery route to administer intrathecal nusinersen in patients with longstanding SMA and spine anatomy precluding lumbar access when done by providers with expertise in this procedure'. • **Germany** – 4 children **Weaver, J *et al.*** (2017) **Transforaminal intrathecal delivery of nusinersen using cone-beam computed tomography for children with spinal muscular atrophy and extensive surgical instrumentation: early results of technical success and safety** Pediatr Radiol (2018) 48:392-397 'Cone-beam CT guidance with two-axis navigational overlay is a safe, effective method for gaining transforaminal intrathecal access in children with spinal abnormalities and hardware precluding the use of standard techniques.' • **Germany** – 20 children **Strauss, K *et al.*** (2018) **Preliminary Safety and Tolerability of a Novel Subcutaneous Intrathecal Catheter System for Repeated Outpatient Dosing of Nusinersen to Children and Adults With Spinal Muscular Atrophy** J Pediatr Orthop 2018; 00:000–000 'In summary, nusinersen via repeated intrathecal injection is effective therapy for all types of SMA, but its standard method of interlaminar delivery poses both absolute and relative challenges for a large proportion of patients. More data are needed to determine if nusinersen has comparable efficacy when delivered by subcutaneous port as compared with the standard interlaminar route. However, our initial observations are promising, and long-term administration of nusinersen via the SIC or similar device has the potential to double the number of children worldwide who can safely receive the drug while simultaneously lowering its long-term administration cost 5- to 10-fold.' 'Although the SIC was designed for SMA patients with advanced disease and attendant spinal pathology, our preliminary observations have implications for younger, less severely affected patients. As private and government insurers adapt to the extraordinary costs associated with new disease-modifying precision therapies, they will likely seek practical innovations like the SIC, which have the potential to safely control administration costs while preserving therapeutic value.' **In summary: we urge NICE to ensure that people whose SMA has created challenges in terms of the delivery of the drug are also given the opportunity to discuss the possibility with their clinicians. The ability of clinicians to explore and implement these options in the UK could lead to new methods of delivery and reduction in costs of delivery.**	evidence. Also, NICE is only able to assess a product within its marketing authorisation.
52	**Consultees (patient/carer groups)**	Spinal Muscular Atrophy Support UK and The SMA Trust	**In summary:** • We are concerned that NICE's apparent over estimation of the population who would want this treatment and for whom it would be clinically safe may lead to incorrect assumptions by NICE as to the total budget that would be required	Thank you for your comment. Responses to each point are found in response to

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			• We ask NICE to include in their evidence base the outcomes of 5 'real-world' studies of 235 patients aged 1 month – 35.7 years receiving treatment via the SMA Type 1 Expanded Access Programme.
			
			• We suggest that real world studies that comment on parent views and our own survey indicate less uncertainty about treatment outcomes than NICE concludes
			
			• We agree with NICE that both the company's and the ERG's approaches to economic models had serious limitations. We understand NICE's decision to use both approaches sought to address this, but are concerned that the final ICER values may not appropriately reflect the impact of the worst health states caused by untreated SMA as reported in clinical and patient expert evidence
			
			• We seek an assurance that NICE's economic analysis covered all the real-world costs of the health and personal health and social services required to support a person with SMA and their family and included the impact of SMA affecting more than one carer. We also wish it to be noted that we consider the model falls short in that it fails to cover the real-world costs that lie outside the realm of health and social services. We are aware this is not possible within this appraisal but consider that this needs to be urgently addressed by NICE
			
			• We contend that due to nusinersen having been assessed via an STA, the ICER threshold is inappropriate and urge flexibility when establishing what will be an appropriate range for a Managed Access Agreement.
			
			• We urge NICE to ensure that England and Wales offer access in line with Europe and that there is no break in the delivery of treatment to infants with SMA Type 1 once Biogen's EAP closes on 1st November
			
			• We identify three clinical sub groups all of whom can be identified in clinical practice. They are all of equal importance as clinical evidence demonstrates they all have the potential of benefiting from treatment. They are differentiated only so that different 'work streams' can be established within any MAA. They are:
			  • Group A: all newly diagnosed with SMA Type 1, 2 or 3
			  • Group B: all with Type 2 or 3 who are at a 'critical point' in terms of the progressions of their SMA
			  • Group C: all with Type 2 and 3 who are not at a critical point but where treatment will potentially bring stability
			• The EAP has ensured that many paediatric centres are ready and delivering treatment. We don't know how ready adult services are to respond to new work streams. Any exercise to collate numbers for treatment must map out location of patients and a plan for ensuring efficient delivery of treatment to all three groups and geographical equity.
			
			• We urge NICE to ensure that people whose SMA has created challenges in terms of the delivery of the drug are also given the opportunity to discuss the possibility of treatment with their clinicians. The ability of clinicians to explore and implement these options in the UK could lead to new methods of delivery and reduction in costs of delivery.
			
			• We are concerned that NICE's appraisal system has led to undue delays and difficulties resulting in England and Wales being almost the only countries in Europe not offering access to what is proving to be an effective treatment for so many with this devastating condition.
				comments 35 to 51 above.

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			• We urge NICE to continue to meet with NHS England, Biogen, clinicians and patient groups to agree a Managed Access Agreement with work streams that will provide access to all with SMA Type 1, 2, and 3 whom we have identified in this response.	
53	**Consultee (patient/carer group)**	TreatSMA	The first serious concern with the draft recommendation is that it seems to restrict itself to the RCT data while ignoring the available real-world evidence (RWE) generated in post-MA clinical use of the drug. In case of clinical research in phenotypically varied ultra-rare disorders like SMA, where RCT data cannot reasonably cover all the disease manifestations, it crucial that all available evidence is considered whilst appraising the intervention authorised in treatment of the entire spectrum of the disorder, consistently with the drug's label. RWE evidence on nusinersen effects across the SMA spectrum, which is increasingly being published in academic journals, is largely supportive of the RCT results, even as it additionally covers other populations. TreatSMA has made it available to the Committee at the consultation stage. In particular, the committee had received studies on long-term effect of nusinersen treatment in patients classified as SMA type 1 older than 6 months. The Committee was also briefed about the real-life benefits of nusinersen treatment in presymptomatic and early symptomatic patients. Furthermore, the clinical experts have highlighted to the Committee during the initial appraisal meeting that their observations indeed correlate to evidence reported by caregivers. For instance, since the 2017 start of the nusinersen expanded access programme at the Great Ormond Street Hospital in children with the most severe form of SMA, not a single child has passed away, for the first time in the hospital's history. We need to note that a recent class-IV evidence by Aragon-Gawinska et al, who analysed nusinersen efficacy in post-MA setting in a sample of 33 SMA type 1 patients aged 8 to 113 months, concludes that the functional improvement due to treatment was unrelated to their age at start of treatment or the number of SMN2 copies (doi: 10.1212/WNL.0000000000006281). We at TreatSMA have anecdotal evidence of similar nusinersen efficacy in 6 adult patients with symptoms consistent with borderline SMA type 1 and 2 phenotype, with an increase of several HINE points ([redacted]) over 6 months of nusinersen treatment. We find this apparent disregard to RWE puzzling, especially considering the rarity of the disorder and the challenges related to generating data across the entire phenotypic spectrum of this monogenic disease. Increasingly, HTA agencies worldwide attach significant weight to RWE, considering it a better predictor of the treatment's effects in clinical practice. In many cases, high-quality RWE is regarded on a par with RCT evidence (several meta-analyses of HTA practice in various countries are available in academic journals). Thus, we suggest that the Committee reviews the draft ACD in consideration of all the available evidence, including in particular published and unpublished data from global clinical practice.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
54	**Consultee (patient/carer group)**	TreatSMA	We are concerned that the negative recommendation seems to rely predominantly on the uncertainty of long-term effects of treatment, in an apparent disregard for the pathological mechanism of spinal muscular atrophy and the molecular mechanism of action of nusinersen intervention. The drug, as evidenced in clinical studies, increases the amount of cell-available SMN protein through modifying the splicing of the SMN2 gene, thus addressing the root cause of SMA pathology (i.e., the deficiency of the SMN protein in motor neuron cells). There is no plausible, scientific reason to speculate that the SMN2-targeting action of this antisense oligonucleotide could stop at one point. Contrary: long-term observations confirm that nearly all patients in whom the drug has been effective continue	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD)

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			improving over years, albeit, naturally, in a variable degree. The short span of the observations in the two phase-III clinical trials did not always show major milestone achievement over the trial duration, however long-term data, including self-reported data, offer no doubt that improvement continues. While long-term data is yet to be generated, as is the case with every new drug, we stress that in view of the drug's mechanism there is no sane reason to doubt that treatment will offer increasing benefits to patients over time.	have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA. Sections 3.13 to 3.16 of the FAD describe the changes to the economic model and the committee's consideration of these.
55	**Consultee (patient/carer group)**	TreatSMA	We are concerned that the model inadequately estimates the disease burden for UK patients and their carers, which in turn likely translates into incorrect estimation of disease state disutilities. The patient and carer health state estimation appears to have been based exclusively on a single study with data collected predominantly in Spain (Bastida et al), a country with an entirely different social care system and significantly lower associated costs; data from other countries than Spain in that study is of low quality and should be avoided in pharmacoeconomic analyses. Rough calculations carried out by TreatSMA and based on data sourced from the UK families suggest that an average disease-related financial burden ranges from around £80,000 a year in SMA type 2-3 to more than £200,000 a year in severe patients (usually classified as SMA type 1 or weak type 2). As an example, a standard basic NHS care package for SMA type 1 that consists of a provision of a single night carer for 10 hour daily carries an associated cost to NHS of £109,500 (3,650 hours contracted at £30/h). Further disease-related costs for	Thank you for your comment. The company's model, including the approach to reflecting utility and costs, has now changed. This and the committee's view

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			the taxpayer include, among others: planned hospital visits, unplanned hospitalisations (including at PICU/ICU – several times a year in SMA type 1), equipment (orthoses, ventilator, cough assist, specialised wheelchair, bed, standing frame, etc., all of which have to be regularly replaced as the child grows), house adaptations (LA packages of up to £50,000), school adaptations, additional school staff member (TA) or, sometimes, specialised schooling, physiotherapy, OT, cost of mobility / car adaptations, and finally, significant loss of earnings for the family (and the cost of associated disability/housing benefits and tax credits that usually have to be provided instead). While not all of the cost would disappear with treatment right away, based on RWE the majority of treated patients are expected to significantly improve functionally over time, with improvements expected to continue for the lifetime of the patient (due to the drug's mechanism of action). Furthermore, early initiation of treatment would in all likelihood prevent functional decline and, consequently, significantly reduce the need for highly specialised care packages. For instance, thanks to preventing respiratory deterioration – which nusinersen has been proven to do in the vast majority of treated patients – the treatment will make the £109,500 night care package unnecessary. Consequently, it is entirely plausible that in some subgroups of patients, the savings brought about by early pharmacological intervention may approach the drug procurement costs even at its list prices. It is worth pointing out that a HTA in even a relatively poor eastern European country Poland has assumed the annual medical and loss-of-productivity costs (excluding schooling, mobility and adaptations) in case of a SMA 1 type patient at approx. £95,000 (PLN 460,018). Summing up, TreatSMA is of the view that the disease burden has been severely underestimated in the company's economic model, whilst the Committee's expressed view that it has been overestimated is entirely unfounded.	of the changes have been captured in sections 3.17, 3.18, and 3.19 of the FAD.
56	**Consultee (patient/carer group)**	TreatSMA	While we understand and share the global outrage at the list price of nusinersen, we need to stress that any pharmacoeconomic analyses that result in allowing or disallowing access to the only effective treatment should be based on the actual purchase price and the effective budget impact. We are aware that the manufacturer has offered substantial discounts and risk-sharing arrangements in other countries. We request that the nusinersen appraisal is reviewed in full accordance with the drug's label based on the manufacturer's full commercial offer.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is

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				now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA. Furthermore, it is essential that the economic model reflects the commercial offer. The model has since been updated.
57	**Consultee (patient/carer group)**	TreatSMA	NICE's continuous reliance on QALY analysis in determining the value of an intervention has been a subject of sustained criticism in academic circles, especially when it relates to interventions in orphan diseases. Currently, out of all EU countries, only UK and Poland use QALY as the principal determinant in reimbursement decisions, with Poland planning to move away from it at least in orphan diseases from 2019. All the other European countries use a QALY value as one of secondary parameters in HTA. Most recently, Scotland has established a separate appraisal pathway for orphan drugs in which the QALY analysis plays a supportive role. This is justified based on a distinct character of the majority of orphan conditions (80% of which are of genetic origin) as well as on different economic considerations related to the development of orphan drugs. We understand that it is not easy to change an established practice, but we, the SMA families, do not want to be hostages of a methodology that has long been discredited and replaced everywhere else with methodologies better suited to appraising orphan drugs. We need to underline that in all other European country, results of technology appraisal of nusinersen in SMA have been positive, which puts an even bigger question mark over the approach used by NICE to the detriment of thousands of those who suffer from SMA.	Thank you for your comment. NICE uses cost per QALY for the estimation of cost effectiveness in line with its published methodology, as one of several decision criteria (see sections 5.3 and 6 in NICE's guide to the methods of technology appraisal). This allows a consistent assessment of treatments across the range of diseases and populations appraised by the committee.
58	**Consultee**	SMA Reach	**Has all the relevant evidence being considered?**	Thank you for

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	(patient/carer group)	UK	In our view the relevant evidence has not been sufficiently considered: When referring to the reported literature, there is no acknowledgement of the fact that in the relevant clinical trials as well as in the already ongoing Extended Access Program (EAP), nusinersen is given to children with already wellestablished disease rather than to those still at an earlier disease stage. This is an important point, as infants with shorter disease duration had a considerably better response both from a motor and (in the case of SMA type 1) respiratory perspective, as has been well-documented in two seminal papers in the New England Journal of Medicine (Mercuri et a, N Engl J Med. 2018 Feb 15;378(7):625-635; Finkel et al . N Engl J Med. 2017 Nov 2;377(18):1723-1732) reporting the outcome of the relevant clinical trials. This observation is not unexpected, as at the advanced stages of the disease motor neuron loss has already accelerated. It is, on the contrary, almost surprising that children recruited at a more advanced disease stage through the EAP in most instances show some - although limited - motor response. If nusinersen was adopted, and became the established standard of care, it would be administered as soon as possible after the diagnosis, and the results would therefore be at least comparable to those reported in the NEJM papers reporting the outcome in children with shorter disease duration. We feel that it is therefore of utmost importance that when the outcome of the relevant studies is assessed, the timing of the intervention is considered in the context of the biology of the underlying motor neuron disease. The only modest improvement observed in children affected by type 1 SMA who start to receive the drug only at a more advanced disease stage is not unexpected, as it would not be unexpected that, for example, an in principle effective antineoplastic therapy will only achieve a modest effect if administered to individuals with already advanced metastatic cancer. It is almost surprising to see that even after a long disease duration, a substantial proportion of SMA patients can still demonstrate motor improvement after nusinersen, as reported by multiple groups reporting the real world evidence from the EAPs worldwide. Clearly the extent of response even in this very advanced population is more variable compared to early symptomatic children, and we urge the committee to apply both the knowledge on the biology of the disease and assessment of all published evidence including timing of drug administration and clinical response. A number of recent papers that provide real life experience of the drug and stress the overall positive experience found by these investigators is reported below Aragon-Gawinska, K et al (2018) A cohort study Neurology® 2018;00:1-7. doi:10.1212/WNL.0000000000006281 Farrar, M et al (2018);89:937–942. doi:10.1136/jnnp-2017-317412 Pechmann, A et al (2018) Journal of Neuromuscular Diseases 5 (2018) 135-143 DOI 10.3233/JND180315 Pane, M et al (2018) Neuromuscular Disorders 28 (2018) 582-585 30 May 201 Mousa, M et al (2018) # Springer-Verlag GmbH Germany, Springer Nature July 2018 Veerapandiyan, A et al (2018) Neurology® 2018;91:e620-e624	your comment. Section 3.10 of the FAD now addresses early administration of nusinersen. Furthermore, the recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
59	**Consultee (patient/carer group)**	SMA Reach UK	**Concerns regarding the long term effect of the drug**. While the committee reiterated multiple times that there are concerns regarding the long-term effect of the drug, there is never acknowledgement of the fact that treated patients in each of the published studies continue to show improvement, and do not appear to peak in their abilities, let alone demonstrate deterioration. The fact that children with more advanced disease and in	Thank you for your comment. Section 3.10 of the FAD now addresses early

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			particular those recruited in a real world setting through the EAP may not experience improvement or may in some instances deteriorate is not unexpected, taking into account the biology of the disease with already accelerated motor neurone loss at this stage. However, as outlined above, this observation cannot be considered an argument for withholding treatment from infants at an earlier disease stage, who have demonstrated robust and sustained improvement in the relevant clinical studies. We need to keep in mind that any drug acting by promoting SMN production will have maximal efficacy in the next generation of patients, as these will be the patients in whom better outcome is expected based on all the available literature and experience. The data supporting this argument are clearly presented in the 2 publications reporting the outcome of the original nusinersen studies (Mercuri et a, N Engl J Med. 2018 Feb 15;378(7):625-635; Finkel et al . N Engl J Med. 2017 Nov 2;377(18):1723-1732.. This lack of acknowledgement by the committee of a slow but continuous improvement in the majority of treated children, while stressing the possibility of long term deterioration, is a concern to us as it does not capture the peer reviewed published evidence.	administration of nusinersen. Furthermore, **t**he recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
60	**Consultee (patient/carer group)**	SMA Reach UK	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** In our opinion the answer to this question has to be “No”. While Biogen, the manufacturing company, may perhaps have provided an overly optimistic assessment of the possible benefits, in our opinion the committee provided a far too pessimistic evaluation. In particular, this evaluation does not at all take into account the experience in children receiving the drug relatively early in the disease, the group of patients which will represent the majority of the treated patients after the current patient population has been treated. If one takes this into account, it could well be that the evaluation from the company represents a closer adherence to reality compared to the view of the committee. Furthermore, we note that the QUALY measurement is not a suitable tool for the evaluation of rare and devastating diseases such as SMA type 1 and 2 using, also reflected in the fact	Thank you for your comment. Please note that the company’s economic model has now changed. The recommendations in the Final

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			that the QUALY measurement has not been used as a tool in other similarly rare and devastating conditions. The individual and societal disease burden that conditions like SMA1 and 2 (and to a lesser extent the later-onset types 3 and 4) carry for is currently not well-captured and generally underappreciated by those not directly affected by these devastating and profoundly disabling conditions. We are also concerned that NHSE and NICE do not have accurate figures on which to take the decision of not having SMA being evaluated via the highly specialised route, which would clearly represent an appropriate route for the evaluation of this type of intervention. The committee appears to recognise that SMA is a rare and devastating condition; to however recommend the blunt QUALY tool for its evaluation, a tool fit for the purpose of common and less complex conditions	Appraisal Document (FAD) have also changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA. Furthermore, section 3.10 of the FAD now addresses early administration of nusinersen. **NICE uses cost per QALY for the estimation of cost effectiveness in line with its published methodology,**

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				as one of several decision criteria (see sections 5.3 and 6 in NICE's guide to the methods of technology appraisal). This allows a consistent assessment of treatments across the range of diseases and populations appraised by the committee. Following extensive discussion at scoping, it was agreed that this topic is appropriate for consideration as an STA.
61	**Consultee (patient/carer group)**	SMA Reach UK	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** The provisional recommendation are not a suitable basis for guidance to the NHS, as by not considering nusinersen treatment, patients with SMA will be deprived of the perspective of improved motor function and prolonged. We do therefore not support these recommendations. We also note that despite the advanced disease stage at the point of recruitment, the fatality in the SMA1 population recruited under the EAP commenced in the UK in August 2017 has dramatically decreased. We have indicated above that motor function improved in the majority of these patients despite the already advanced stage of disease at the time nusinersen treatment was commenced. We can also report that in some of the children who have been recruited more recently following a shorter disease duration, a reduction of respiratory requirements could be observed. These data were discussed and presented at a national workshop organized by our group, involving paediatricians, paediatric neurologists, respiratory physicians and physiotherapists, and intensivists from the entire UK We also note that the commercial availability of Nusinersen for SMA 1 in Scotland brings equality challenges that families and physicians will be forced to face given the current NICE recommendations. Given the announced decision from Biogen to	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the

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			terminate in November 2018 the EAP for SMA1 after 2 years from its inception, this will represent discrimination against families living in England and Wales	views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
62	**Consultee (patient/carer group)**	SMA Reach UK	**Are the boundaries between different subtype of SMA clear or blurred.** We do not agree that the boundaries are blurred, as SMA subtypes are diagnosed according to clear clinical criteria, recognised for centuries and the maximal functional abilities that inform these clinical criteria are typically reached at the time of the diagnosis in the overwhelming majority of patients. For example, at the time of diagnosis, essentially all patients with type II SMA would have already acquired the ability to sit (an exclusion criteria for SMA1) and patients with type III SMA would have acquired the ability to walk (an exclusion criteria for SMA1). It is correct that in exceptional cases there can be some patients who are on the clinical boundary of two different subtypes (for example a child, “almost able to sit”), however, these cases are rare, and an expert clinician should be able to recognise these rare exceptions.	Thank you for your comment. It was the opinion of the patient and clinical experts that boundaries between different SMA classifications are blurred - section 3.2 of the FAD acknowledges that it is the best classification system available.
63	**Consultee (patient/carer group)**	SMA Reach UK	**Requested comments on whether there is a clinically distinct subgroup of people in whom nusinersen is expected to have better efficacy.** As indicated before, the published literature suggests that SMA type I children with a shorter disease course clearly benefitted more than children with longer disease duration (Finkel et al, NEJM2017); comparable findings have been documented in children with type 2 SMA (Mercuri et al, NEJM 2018). For conditions like type 3 SMA the less aggressive progression most likely indicates that the window of opportunity for improvement is even wider. Of note, between 80-90% of children with type 3 SMA with onset before the age of three years (classified as SMA 3a) will lose their ability to walk by their late teens, emphasizing the need for therapeutic intervention also in this group. In a recently presented and already publically available long term extension study of 14 children with type 3 SMA originally recruited in the nusinersen clinical trial, the median (25th,	Thank you for your comment. The responses to NICE’s specific questions on clinically distinct subgroups fed into a workshop conducted by NICE to discuss

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			75th percentiles) distance walked increased over time by 17.0 (0.0, 51.0) meters at Day 253 , and by 98.0 (62.0, 135.0) meters at Day 1050 (Montes et al, 2018, Cure SMA meeting proceedings). These figures contrast with all published literature on the natural history of children with SMA3 and demonstrate that the nusinersen effect, if anything, builds up over time	these issues with clinical and patient experts. Furthermore, section 3.10 of the FAD now addresses early administration of nusinersen.
64	**Department of Health and Social Care**		No comment	N/A
65	**Commentator (clinical expert and carer)**	Elizabeth Lockley	I am concerned that there are lots of children (including my type 2 son) who are receiving NO treatment. They have NO other option. As a consequence, these **children are getting weaker as they grow**. **This increased weakness is going to create more health, physical, emotional, medical and care needs** which in turn will increase already under estimated care costs. Type 2 children are already expected to be able lead long lives with fulfilling careers. With treatment these children could achieve this more independently, have less care needs and avoid major medical interventions. For example, if a patient had enough arm strength to self-transfer on / off a toilet this would avoid the need for hoisting systems and carers. Or if they had enough muscle strength to support their spine as they grow, then invasive spinal surgery and increased hospitalised for chest infections could be avoided.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the

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				context of a MAA. Furthermore, section 2.8 of the FAD now highlights the importance of small improvements to patients and families while section 3.17 highlights that the utilities may not have captured added benefits of obtaining particular motor skills (such as those mentioned in the comment).
66	**Commentator (clinical expert and carer)**	Elizabeth Lockley	**I feel that the cost effectiveness of this drug has been hugely underestimated.** A lot of the care needs and medical and equipment costs are swallowed by the patient's family, including the potential sacrifice of careers. Also, the smallest gains in strength, which may seem insignificant, could dramatically change a life and increase independence. (E.g. the strength to operate a joystick on wheelchair or a tablet.)	Thank you for your comment. Section 3.3 and section 3.19 of the FAD have been amended to emphasise the impact on family members and underestimated costs of living with SMA. Furthermore, the recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the

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				consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
67	**Commentator (clinical expert and carer)**	Elizabeth Lockley	**<u>Sub groups</u>** I agree that types are NOT an accurate way of grouping patients. Boundaries are blurred between types and can be subjective. Also, now some Type 1s on the Early Access Programme are becoming stronger and are now achieving milestones which would clinically class them as Type 2s. Evidence suggests the sooner the patient is given the drug the more benefit it could give. However, I do not feel that anyone should be denied a drug that could benefit then. It will be extremely difficult to draw the line anywhere. I am aware that during periods of rapid growth (e.g. puberty) patient's decline can be exacerbated and they can weaken further. Therefore, it would be good to have treatment pre-puberty to avoid this. However, different children go through puberty at different times and denying post puberty patients the drug could also add to teenage angst and create further problems. I feel the only initial option is to offer to ALL types and ALL ages for at least a determined trial period	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is

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				now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA. Furthermore, section 3.10 of the FAD now addresses early administration of nusinersen.
68	**Commentator (clinical expert and carer)**	Adnan Mansur	The scientific data for efficacy of nusinersen, is recent. My recommendation is below are based on the scientific data and deduction from first principles of management of SMA, and the underlying pathogenesis. My suggested priorities in terms of need and effectiveness are listed below: 1. spinal muscular atrophy type I, especially new onset cases 2. spinal muscular atrophy type II - under 3 years of age 3. spinal must atrophy type IIIA (onset of symptoms under 3 years of age) . When they are in the first 3 years of life (or 4 below) 4. SMA type III , with worsening of motor function and risk of loss of walking 5. SMA1 and 2 infants, in the presymptomatic phase, diagnosed on the base of genetic testing, in families where there was a previous history of spinal muscular atrophy. In practice, this would mean offering the treatment to SMA infant's with SMN2 copy number of 4 or below Category five, though listed at the end and anticipated to have small numbers, is a priority, as it is likely to prevent or significantly significant ameliorate disease symptoms which would develop later in future	Thank you for your comment. The responses to NICE's specific questions on clinically distinct subgroups fed into a workshop conducted by NICE to discuss these issues with clinical and patient experts.
69	**Web comments**	Carer 1 (Parent of sma type 2 child)	This drug is so important to all the parents who care for sma children it's not fair for them to live like this when there's a drug out there that can improve there life it shouldn't even be a question to not having it we should ! Despite the money it costs improving a sma child's life & health outweighs anything	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients,

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				carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
70	**Web comments**	Carer 2	You state that there are is no long term evidence for this treatment, however, the trials lasted 5 years and the drug was fast tracked by the FDA because of the benefits it showed during the trials, and was also fast tracked by the EMA in May 2017. I don't know how long the panel thinks trials should last when they have shown significant benefit to a population of patients who do not have any other treament approved for SMA You state that there is an unmet need for effective treatments that could slow progression, but by denying this treatment which is an effective treatment you are not meeting the needs of the patients You stated you considered a wide range of factors while appraising Nusinersen, one of which was for end of life treatments. This is a facor which is considered for cancer patients and has no bearing for the treatment and consideration of a treatment for a RARE condition You say that Nusinersen cannot be recommended due to cost effectiveness, but you do not state what would be an effective cost? Surely there must be a threshold where you would consider it to be cost effective, and this has to be discussed between NHS and Biogen You mention that you also considered a proposed commercial arrangement. What was this arrangement, and if this was not suitable, surely this was the time to discuss one that would suit? You state that people with type 2 are often severely disabled and unable to walk unaided. The truth is that type 2 patients are unable to walk at all. Maybe the committee should have the proper data before they appraise? Patient experts described the blurring between the types often leading to a misunderstanding of the condition. Clinical experts accepted this but decided that the current classification system is the most accurate predictor. How can you say this when patient experts who deal with many SMA patients every year have a better understanding of the condition than you do? The committee acknowledged that Nusinersen should be considered for all types as per it's marketing label, but then	Thank you for your comments. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2,

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			commented that Biogen had no data for types 0 and 4. When they looked at the data surely they would know that the trials were only taken place for certain types and therefore in my opinion you are picking at any little thing that may make this medication look bad, and in my opinion this is disgraceful. It clearly states that 51% of patients in the ENDEAR trial reached motor milestones compared to 0% in the sham group. In fact this trial was stopped early and all children put on Nusinersen because it was unethical to keep them on a sham treatment when the actual drug was so effective. Surely this indicates that this treatment is effective Again the committee doubts the long term effectiveness of this treatment. So is it ethical to just not recommend it and withdraw it from a population who need an unmet need for some kind of treatment. Surely it would be better for patients to try it than to not have access at all? The committee said it was plausible that SMA left untreated would worsen but implausible that SMA treated with Nusinersen could not get worse, as some patients treated with the drug still got worse. Surely this indicates that the treatment may affect on an individual basis so therefore every patient should have the right to at least try it and possibly put stop criteria in place if the patient has 2 appointments where there is no improvement in any of the scales. so you could say 2 years or 9 injections, if no improvement then the treatment is stopped? The committee also heard that the population eligible for Nusinersen includes people with disabilities. Really? I thought that this would be obvious and wouldn't have to be stated. So could we argue that based on people being disabled, you have refused the treatment on these grounds, so therefore it is discrimination? The committee stated that Nusinersen met the end of life criteria for early onset SMA but not for the later onset. I think it should be pointed out that it is not all about extending life. Nusinersen has been proven time and time again to improve the motor and respiratory function of SMA patients. Although you keep stating there is no evidence that it prolongs life, surely the fact that patients improve in other ways and can in fact have their life improved by any slight motor function improvements, which will then open up a whole new life by being able to access touch screens, powered wheelchairs and being able to move a finger or hand to enable them to communicate with others through different media sources is better than not giving them the treatments at all.	and 3 SMA in the context of a MAA. NICE are required to appraise technologies within their marketing authorisation. The committee acknowledged that the available clinical evidence was for SMA types 1-3, so restricted its recommendations to these types of SMA NICE requires the costs and benefits of a treatments to be considered over the lifetime of a patient (see 5.1.5-5.1.7 in NICE's guide to the methods of technology appraisal). Within this timescale, long-term evidence on benefits was lacking from the clinical trials. End of life

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				considerations may apply for any condition where treatment may extend life – criteria can be found in section 6.2.10 of NICE's guide to the methods of technology appraisal. The maximum acceptable ICER is £20,000-£30,000 per QALY, as described in section 5.8.10 of the NICE's method guide (link above). Section 3.1 of the FAD has been amended to better reflect the severity of type 2 SMA. Section 3.2 of the FAD notes that clinical experts consider that the current classification system is the best classification system available. Section 3.6 (now

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				3.7) of the FAD acknowledges that the ENDEAR trial was stopped because of the strength of benefit. Stopping criteria for the treatment is included in the managed access agreement (see section 3.22 of the FAD). The purpose of assessing whether or not nusinersen meets end of life criteria is because the Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. For example, the committee can consider QALY weighting in these instances (see sections 6.2.9 - 6.2.12 of NICE's methods

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				guide linked to above).
71	**Web comments**	Carer 3 (parent)	Our son, [redacted], is two years and 10 months old and has SMA type 2. [redacted] SMA has had a massive impact on all of our lives; from the age of 12 months when he began to become reluctant to stand, after previously loving exploring our house as he crawled around, through the early days of diagnosis aged around 16 months, up until the present day. SMA will progressively affect every single muscle in his body. Right now [redacted] can sit and play, but his muscles have slowly lost the strength to help him stand, crawl or walk. He can lift his hands to raise a spoon or cup to eat and drink, but is beginning to find it difficult to raise his head should it flop onto his chest. He cannot roll or move in bed when he sleeps. He needs daily medicine to help him with chronic constipation. He also uses a cough assist machine each morning to help clear his lungs as his breathing is compromised by his condition as he cannot fill his lungs adequately. He is completely dependent on us, his parents, for every aspect of his care. Yet perhaps the worst part of his condition is the knowledge that as he grows, each and every day he will get weaker. His current situation will only worsen. He will not gain skills or new abilities like other children. Photographs will not show him growing stronger, they will show what he used to be like, and that he was stronger in these photos than today and we know that tomorrow he will be weaker. This knowledge is an awful emotional burden for us all, [redacted], his parents and wider family, to bear. We are watching our son slowly slip away from us; can you imagine anything crueller? Because we have a positive attitude to SMA we will not give up. We just get on with our lives as best we can, but sometimes it's important to reflect on the extra challenges we face. Since November of 2017 we have endured 6 emergency hospitalisations for chest infections. We have managed just as many infections at home. Each time [redacted] has to undergo a variety of painful and stressful procedures, such as nasal and oral suction, tube feeding and rigorous physiotherapy. We have multiple appointments with a myriad of medical professionals: orthopaedics, orthotics, respiratory, occupational therapy, dieticians and neuromuscular departments to name just a few. As his lumbar muscles weaken he is developing a scoliosis and uses a variety of supportive orthopaedic seats. Our house is full of equipment, like standing frames, supportive play chairs, adapted baths as well as a motorised wheelchair. We will be adapting our home to improve access for his wheelchair, as well as modifying the garden to give him the opportunity to explore the space independently. We are now awaiting a BiPAP assisted-breathing machine, which will require [redacted] to wear a mask but will help him fill his lungs more effectively, adding to the list of interventions this beautiful 3 year-old boy has to face on a daily basis. Finally, all trips and excursions are meticulously planned; will he need his cough assist? What medicines will he need? How will he sit? What chairs do we need? What toilet facilities are there? [redacted]is an incredibly bright, articulate and intelligent child; he is constantly amazing us with his insight and memory for detail. He is becoming more self-aware, and he is learning that he is different and he cannot play with his friends like he wants to. He loves going to nursery three days a week and has many friends who love him and miss him when he is sick, which unfortunately has been far too often. He has the right to an education like every child, and is learning so much, so quickly. We all believe, family, medical team and teachers, that [redacted] has a bright future, but that all depends on how we can battle this punishing condition. We know that without treatment, [redacted] will become progressively weaker as he grows up. We know that his life will become harder, and in all likelihood, shorter. His breathing will become more laboured, his swallow less strong. He might need a colostomy bag. He might need breathing support 24 hours a day. His quality of life will worsen steadily. Nursinersen gives us all hope for a better future. From our SMA friends at home and around the world, we know the impact that the drug can have and, while we know that its effects are still being understood, we are desperate to give [redacted] the chance he deserves.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.

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			[redacted] looks like so many of the type 2 children we see in America, in Europe or Australia, with their familiar thin arms and legs and folded bodies, yet still they beam, with beautiful sunny smiles. And to see those children, with type 2, improving, pushing to stand, to walk, to cough more strongly or to raise their heads, as the Nursinersen strengthens them is a miracle. Yet it is a miracle we, in this country, are being denied. We want the opportunity to try Nursinersen, and as [redacted]parents we will do everything in our power to make it happen. We strongly urge NICE to reconsider their decision, for the sake of our son, and for every person and family in the UK suffering with SMA.	
72	**Web comments**	Carer 4 (grandparent)	My Granddaughter has SMA type 2 - she will be 3 years old in November. Since diagnosis in January 2017, we have seen the SMA Community campaign tirelessly for access to SPINRAZA for all those who would benefit. The consultation paper is obviously disappointing in that NICE are not recommending SPINRAZA for funding by the NHS at this stage. We note however that NICE's consultation paper encourages the possibility of a Managed Access Agreement and that talks are taking place with NHS England and Biogen. There is no doubt that the current price of SPINRAZA is expensive but surely it should be weighed against the cost of hospital visits, medication, machinery and the involvement of a multi-disciplinary team for someone who does not receive SPINRAZA. It is obvious but disappointing that SPINRAZA is too expensive to be assessed under the Single Technology Appraisal route. However, it should also be considered that apart from the first year of treatment, the current price of Â£225,000 falls below the HST limit. It would therefore seem that there must surely be some room for negotiation. At nearly 3 years old, My granddaughter is now old enough and bright enough to realise that she is different to other children. My Granddaughter attends full time Nursery and never gives up trying to be independent but her frustration and sadness at not being able to walk and do as others do, is increasingly evident. Of course, we have no answers for her. It should also be borne in mind that SMA does not just affect the patient. Her parents struggle every day with an unpredictable and often hopeless situation, in the face of which they still strive to provide her with the best quality of life that they can. As many parents do, they both work full time and have to manage this around hospital admissions and appointments with various experts within a multi-disciplinary team on an ongoing basis. This is both time consuming and at times, soul destroying. For us as Grandparents, it's an incredibly difficult and impossible scenario. As much support as we try to provide, our son and daughter in law are devastated and we see our Granddaughter struggle every day. The long term psychological and physical effect on both her parents, the family and us are quite apparent. Since her diagnosis in January 2017, good quality sleep and rest are bygone and impossible luxuries. We are consumed with trying to make things better, but for us and other families like ours, there desperately needs to be a light at the end of the tunnel. We are all well aware that SPINRAZA will not cure SMA, but as parents and Grandparents, we want to know that our granddaughter and all children like her, are given the best possible chance of quality of life and survival that it is possible to give. For these reasons, we would ask that NICE reconsider their position to do everything possible to allow SPINRAZA to become available as soon as possible for SMA of all types.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA. Nusinersen is being assessed

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				under the single technology appraisal (STA) process. The evaluation of the technology involves comparing treatment benefits and treatment costs (including other associated costs) of nusinersen against best supportive care. Section 3.3 of the FAD has been amended to emphasise the substantial effect of SMA on multiple members of the family.
73	**Web comments**	Carer 5 (Parent of an under 18 with SMA)	I am writing to you regarding access to the spinal muscular atrophy (SMA) treatment called Spinraza for those under 18 years of age in the UK. Spinraza is the first and only treatment for patients with the rare inherited muscle-wasting condition spinal muscular atrophy (SMA). There are up to 1,300 children and adults living with SMA in the UK. For those who do have the condition, such as my three year old daughter, life without this treatment leads to muscle degeneration resulting is the loss of ability to walk, swallow and breath. There are also significant social, emotional, and financial implications for caregivers such as my wife and I. Spinraza has been licenses across Europe, including the U.K., since June 2017. Children in other countries where the drug is funded, such as Australia, America, the Nordics, and much of Europe, have shown life changing improvements and in many cases the ability to live a normal and productive life. In essence the lack of funding makes the U.K. seem a third world country when it comes to the provision of new medicines. This is increasingly strange when the government is advertising that it is putting billions of pounds of additional money into the NHS. Even Greece and Portugal, both of which have much lower per-capita incomes than Britain, completely subsidize Spinraza for patients.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and

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			The NICE evaluation says that the drug provided a substantial clinical benefit. When I see the benefit those with Type 2 SMA have gained, including the ability to walk and run, in U.S. after being treated with Spinraza, I believe the NICE assessment to be a gross under estimation. This is a devastating disease which forces family and caregivers to watch the slow degeneration of a child to the point they can no longer move and die. Please could we ask you to reconsider the NICE recommendation to include all children under 18 years of age.	clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA. Section 3.3 of the FAD has been amended to emphasise the substantial effect of SMA on multiple members of the family. Section 3.17 of the FAD notes committee conclusions that utilities may not have captured added benefits of obtaining particular motor skills. The current recommendation is not restricted to any age range.

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74	**Web comments**	Carer 6 (parent)	My son is 16 years of age and has SMA 2. The impact on our lives is devastating. [redacted] relies on me and his dad for all his personal care. He requires moving in bed at night frequently(at least once an hour) which has a knock on effect on our days, tempers and energy. As a result we both could no longer work so his dad is now at home full time, decision based on income rather than personal desire. We have at least 1 appointment a week either to a hospital or a health visitor to the home. Last year he couldn't do a full week at school because of ill health and appointments so one of us needs to be full time carer. Then we moved house because our last house couldn't be adapted for [redacted], this move came at a huge financial cost to us. Holidays as a family are expensive because of all the additional equipment plus adapted accommodation isnt easy to come by for a family so we book way in advance and 2 out of 3 times have been cancelled last minute as he becomes unwell. His brothers put up with a lot because of SMA as they miss out [redacted] social group is nil since turning 15/16 as the gap between his abilities and his friends became too large to bridge. Parties, getting on a train to head into town, hanging out at a friends needs planning and an adult, actually any trip involves a lot of planning and cost. [redacted] feels the cold more especially his hands, so we have handwarmers and heating on. He doesn't like getting dressed or undressed unless the room temperature is tropical. He has me and his dad plus his brothers as main carers. We cant go out as a family now because he needs to be close to equipment should he suddenly have chest problems to date his dad and I haven't been out together in 6 years alone. The impact SMA will have without treatment is a continued downward trajectory. [redacted] lost his swallow this year and we can see he is now having difficulty keeping his head up. His cough is not as strong as it was 12 months ago. He has all the emotions of a teenager, doesn't believe he has a place in this world and I have to be hard on him to get him to believe he has a future. Though in my heart I am not sure how long his health will hold out. Knowing there is a treatment and not having access was like having [redacted] diagnosed again and so hard to accept, too hard to accept. My son is bright, funny and handsome I see his old friends who have half of his personality moving on with their lives and my wonderful son who has put up with so much is having his body turn into a prison. Its unbearable some days.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA. Section 3.3 and section 3.19 of the FAD have been amended to emphasise the impact on family members and underestimated costs of living with SMA.

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75	**Web comments**	Carer 7 (parent)	Clearly there is no long term evidence as nusinersen is a new treatment for a chronic disease. I understand there is now data (albeit outside the RCT setting) out to 5 years from the first recruited trial participants. Was this discussed? If not, why not? It would be limited but informative on longer term effects. I cannot emphasize this enough, sma is a devastating diagnosis that destroys the quality of life of an entire family My child has SMA 2/3 and was symptomatic at 18 months. She has now received 5 doses of nusinersen. We sought treatment in the USA and felt we had no choice but to leave our home and family. It was that or watch our beautiful daughter fade away. A negative opinion by NICE would mean that we would be unable to return to the UK and, when we are ultimately obliged to, we will have to watch her slowly loose the strength and function she has gained and explain to her why she can no longer have her 'magic medicine'. Lack of treatment would mean additional appointments to supervise her decline, increased respiratory issues, difficulties attending mainstream schooling, little social opportunities with friends (her or us) and the need for an adapted home when the time comes for a wheelchair. Ultimately she would need ongoing care and an adapted home as an adult. I would not be able to maintain my current employment even part-time with these additional demands and would become a full-time carer on a permanent basis. Receiving an SMA diagnosis for your child is utterly devastating. All the hopes and dreams you hold for your child are replaced by the certain knowledge that they will loose their strength and independence. The measureable and sustained improvements we have witnessed after only 5 doses have given us hope and we are confident that as long as we can access treatment her future is once again bright and shiny. Here is the US, nusinersen is the norm, SMA is no longer a devastating diagnosis. Once the roll-out of newborn screening is complete then SMA will effectively cease to exist as newborns will be treated at birth never developing symptoms. I have worked in HTA for over 15 years now and for the UK to falling so far very behind the US, europe and Australia the system is clearly not fit for this purpose.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA. Section 3.3 of the FAD has been amended to emphasise the substantial effect of SMA on multiple members of the family.

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76	**Web comments**	Carer 8 (parent)	As the mother of a 33 months old with Type 2 SMA, I am heartbroken by NICE's recommendation. I understand that Biogen's price tag for the drug is exorbitant, and I understand that the NHS has funding concerns, but how much is a child's life/quality of life worth? When the NHS is wasting lots of money in bad management and administration (which I have personally witnessed - alongside some very good people doing a fantastic job), when the NHS/NICE pays for the treatment of conditions which are self inflicted and is considering covering the cost of e-cigarettes, when they will pay for IVF treatment for babies to be produced against what mother nature would do, where is the fair use of funds in that. I could explain again the impact of this condition on my daughter but I have already submitted evidence to NICE for the first stage of the consultation and I know that Treat SMA and the SMA charities made it very clear to NICE already, so I have lost the energy to repeat it again. My heart is broken knowing that there is a medication available that would very likely enable my daughter to walk (words of the leading SMA specialist in France), that would slow down the progression of this horrible condition, that would allow her to not rely on me or someone else to wipe her bottom for the rest of her life, to take her to ICU when she gets severe chest infections, to pick toys up when she drops them, but no, I cannot give it to her. I hold the drug company most in contempt for the price tag they have put on it, but also feel ashamed by the choices of what is and what isn't provided by our national healthcare system.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
77	**Web comments**	Carer 9 (parent)	SMA affects quality of life for patients and families: Social affects. Our 5 year old son is unable to attend other childrens' birthday parties and social events if they are inaccessible or inappropriate (e.g.; soft play centres). He often cannot go to friend's houses or attend sleepovers due to steps, stairs, carpets and night-time care required. As a family we are limited to where we can go for days out, holidays and social events. Effect on siblings is also severe, but dependent upon how much additional support is available. If your child has had access to Nusinersen. Age 5, UK diagnosis severe Type 2, French appraisal strong Type 1. Symptomatic from 3-4 months. Treatment started at 4 years 2 months. No further weakening. Gained in strength and movement. HMF prior to treatment around 10. HMF 6 months after treatment 18. Score 18 maintained at 1 year. Slight curve to the spine has reduced.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the

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			* Since treatment no hospital admissions. 4 admissions prior to Nusinersen. * Sleep patterns variable (from 1-6 wakes nightly) but significantly lower since treatment (usually 2) and now able to roll from side to side in bed. * Social opportunities are improved and broader due to increased stamina, reduced fatigue and improved confidence * Getting around is easier (no longer falls in car seat, can travel in wheelchair due to increased muscle function and improved head control). Able to manually propel lightweight wheelchair for longer and further indoors and manage outdoor use of power chair for a full day. * Mental well-being. Feels healthier, stronger and happier. Stronger voice and improved ability to communicate. Able to do more inclusive activities and achieve more on a personal level has improved confidence. Now able to eat publicly without fear of aspiration (inclusion at school lunch and eating at social events). Feels hungry, asks for food, less need for gastrostomy feed everyday. Caring responsibilities -mother, father, sibling, grandparents, 1:1 at school Treatment over 14 months, 7 doses. Physical milestones: -rolling prone-supine-prone -independent sitting with hands free -able to lift head prone on gradient wedge -raise arms to head	consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA. Section 3.3 of the FAD has been amended to emphasise the substantial effect of SMA on multiple members of the family.
78	**Web comments**	Carer 10 (parent)	My main concern is that you are heavily basing the fact that you will not recommend nusinersen due to the lack of evidence of long-term benefit coupled with the high cost. The long-term benefit should not be an issue as it is highly likely that other drugs which are going through clinical trials (e.g. AVXS-101, RG7916) will be more effective and less intrusive (as current results would lead us to believe) and therefore the administration of nusinersen should only be required in the short term to save lives and stop (or at least slow) the degenerative effects of SMA which studies have shown to be the case. Nusinersen is needed now not in the future!! In terms of cost it would seem that Biogen (from their press releases) are more than willing to discuss price structures which would hopefully satisfy all parties (although as NICE have given no real indication to us, the SMA community, on exactly what would constitute an acceptable cost this is hard to gauge). This also raises the question of why so many other European countries most with far less GDP per capita than the UK are able to provide this drug to those that need it? What deals have they managed to broker with Biogen that are acceptable to both?	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments

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			We should also consider the moral obligation that a tax funded institution (NHS) has to provide treatments that are available to treat a condition which is life threatening? In terms of the impact personally please consider the following if you are in any doubt of how destructive SMA is (although I would hope in order to come to your current conclusion you already understand the full implications of the effect of SMA on a person and their family and friends??): On a daily basis our son is affected by SMA as he requires help sitting up in bed, getting dressed, showering, preparing food, getting in and out of the car, the list goes on. Practically all of these things he could do 12 months ago. More recently he is having trouble swallowing and coughing, his life and his dignity are disappearing, shriveling before his and our eyes. He is, and has been for a while, on daily strong painkillers, salbutamol (which is having less effect over time) and St. John's Wort to try and boost his mood. He now has regular appointments with a psychologist who is trying to help him understand his condition and how to cope with it. He also tries to participate in physiotherapy but this is becoming more difficult for him and less effective. So just from this you can appreciate he is constantly utilising NHS resources especially when you start to add occupational therapy, physiotherapists, consultants etc .... things which may be alleviated or reduced if he was given Nusinersen. While you pontificate and make immoral decisions we sit and watch as our son gradually gets weaker and weaker, as his boundaries close in on him and his mental state deteriorates. This disease affects not only the patient but so many people around them as a recent study in Australia highlights (see https://bmjopen.bmj.com/content/8/5/e020907). Please re-consider your initial decision before more die and the lives of so many other for whom there is a real alternative through nusinersen become even more unimaginably difficult.	including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA. Section 3.3 of the FAD has been amended to emphasise the substantial effect of SMA on multiple members of the family.
79	**Web comments**	Carer 11 (parent)	My daughter has SMA Type 2 , she was diagnosed at 16 months and is now 22 years old. We are devastated to hear that the only potential treatment which has become available which could make her life a little easier to live she has been denied access to by NICEs decision to not approve the drug. She was never given the opportunity to access the drug because of her age and her diagnosis Every minute of her day and night is affected by her condition since every function of her body has become progessively weaker over the years . the only part of her body which has remained completely unchanged is her brilliant brain. Every day for 22 years she has had to relie on her family to undertake all her personal care , hoist her from bed to wheelchair to loo to bath , dress her , brush her hair , prepare and cook all her food , cut it up for her , carry her bags , transport her to wherever she wants to go and remain with her since she is reliant on others. With very little muscle strength she uses all of her energies to sit upright , move her arms as much as she can (which is only a few centimeters forward) for the most simplest of tasks which all others would take for granted. She cant even open a packet of crisps.She realises this treatment would not enable her to walk again because the deterioration in her whole body is so extreme but the chance to be less reliant on carers to do the day to day tasks of life would do so much for her self esteem and her quality of life . To be able to increase her lung function which is now at 25 % would be enormous - not be reliant on using a cough assist machine countless times a day never mind the endless hospital appointments which has affected the whole family and other siblings.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the

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			Given the opportunity to maybe regain a little bit of extra power and strength to someone who has very little to start with is enormous to them even though it seems miniscule to the rest of us , Put ourselves in her shoes , its hard but i will fight all the way for her to have access to anything and everything which could make her quality of life better and I sincerely hope the NICE , NHS and the drug company can come to an agreement to make this only treatment available for this life limiting condition available to all that need it .	views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
80	**Web comments**	Carer 12	Before Spinraza Life Expectancy 2 years. Detrimental emotional impact on all family After Spinraza Longer life expectancy, bright future, hopes and ability to make plans, improved mental health of us all. Before Spinraza Unable to support his own head, little strength and movement in his limbs unable to socialise. Laid down most of the time. After Spinraza Controls his powerchair, holds his head easily. Independence, social skills, interaction with others. Before Spinraza Losing his swallow, inevitably would have needed a peg. After Spinraza Eats orally safely, enjoys mealtimes with family, learning to feed himself. Before Spinraza Required constant help to hold and support toys etc. After Spinraza Plays independently with toys, books, paints, learning to write. Before Spinraza Delay with speech After Spinraza Speech has developed inline with his peers, increase in volume, forming sentences. Before Spinraza Most of the time laid down unable to interact with others After Spinraza Enjoys nursery, baby groups, playing with other children, can easily turn his head and takes part in social situations. Before Spinraza	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for

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			Doubtful he would be strong enough to take part in school After Spinraza Starts mainstream school in two years. Before Spinraza Weak chest function, susceptible to chest problems. After Spinraza Development in respiratory function. No hospital admissions	pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
81	**Web comments**	Carer 13 (Parent of a child with SMA Type 1)	Our Son [redacted] has Type 1 SMA and has been receiving Nusinersen since August 2017. We believe that this drug has had a significant positive impact on both [redacted] and our lives for the following reasons: 1. [redacted] deterioration has stopped and we have seen improvements in movement that we would not have expected to see in a child with type 1. 2. [redacted] has had no hospital admissions since starting Nusinersen despite having several chest infections - he is a lot stronger in his abilities to manage and fight these infections without intensive medical intervention. 3. In terms of movement, [redacted] has experienced increased movement in his fingers, hands, wrists, feet, head and facial expression all of which have contributed to his increased abilities to communicate and interact with the rest of the world. 4. [redacted] uses a ventilator when asleep and since starting to receive Nusinersen we have seen ongoing reduction in both his supportive pressures and also his reliance on his ventilator - [redacted] has recently managed a full night without ventilator support (under a sleep study environment) - something we never thought he would be able to do. 5. Due to [redacted] deterioration stopping and his condition becoming more stable this has significantly improved his quality of life. [redacted] increase in strength and resilience has meant he is able to go out more and enjoy quality time with his family including going on holiday for the first time. In addition, we are now in a position that we are looking at schooling for [redacted], again something we would not have even considered pre Nusinersen. 6. [redacted] lack of hospital admission has had a significant positive effective on his family as any period of admission is both stressful and incredibly difficult for us as a family unit ([redacted] has a twin Brother and elder Sister) 7. Since starting to receive Nusinersen [redacted] has become more energetic and less prone to lengthy periods of sleeping - this means [redacted] is more willing to engage in activities and now has more structure to his day as he has a regular sleeping pattern. 8. [redacted] can now sit upright (within a fully supportive seating system) for extended periods of time which is improving [redacted] posture and allowing him a different perspective on the world other than his usual prone position [redacted] is one of the lucky few to be receiving this life saving medication in the UK and though we fully appreciate the financial burden of this drug to the NHS the positive life saving outcomes must outweigh the cost. We hoped for a slowing in [redacted] deterioration, what we have experienced with Nusinersen goes far beyond our hopes and has potentially saved our son's life.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
82	**Web comments**	Carer 14 (Parent to child with SMA Type2)	I am writing as a parent, our youngest son [redacted] was diagnosed with SMA Type 2 last November at 18 months. He turned 2 years at the end of May and during the last 6 months, we have seen a big decline in his ability to do things. Despite regular physio, hydrotherapy, Hippotherapy and purchasing numerous pieces of equipment to help his overall support, the degenerative state of this condition is stealing the ability for him to complete general daily tasks like brushing his teeth, holding	Thank you for your comment. The recommendation

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			his cup to drink and eating his food. His reach is now limited, he can no longer put his hands on his head for a sing a long to "head, shoulders, knees and toes. It's heartbreaking. Having recently been on holiday, sitting watching the significant difference between our two sons (We have a 6 year old son too, [redacted]) it's devastating and eats away at us daily. We have to sometimes restrict what [redacted] does as we don't want [redacted] to feel upset he can't do something - e.g going to a trampoline/Park play area. So [redacted] misses out, grandparents who care for [redacted] whilst I work part time have to travel to us as all the equipment is at our house that [redacted] needs and we can't afford to buy a 2nd or 3rd set for their houses too. It splits the family up, e.g on holiday, our eldest son was so keen to go down to a beach to the rocks pools (only accessible by steps) he went with Dad whilst I waited with [redacted] at the top in his powerchair- it was awful when he so desperately wanted to join his older brother. I am actually sat in a foreign country right now as I write this trying to get our son on a drugs trial whilst my partner and [redacted] are at home, how sad I shall miss [redacted] returning to school. It kills me. Why should we have to do this?! Tell me?! His need is 24/7, it's like having a new born baby that doesn't even sleep during the day (for you to have a little rest), he wants to learn, he wants to explore, he's not content with just a few toys as his brain is well and truly working but he requires help, pressing buttons, opening lids, reaching for things, turning pages, moving, lifting, getting comfy. It's utterly draining both physically and mentally but he never asked to be born with this. Everything is a battle to get equipment, to get adaptions made around the house, to get appointments booked, we have to fundraise, which doesn't sit comfortable with us, but we don't have any option. It's literally a full time job, filling out paperwork, attending appointments, chasing appointments, waiting in for equipment to be delivered, attending fundraising events, daily physio, weekly hydro, weekly hippotherapy, whilst still trying not to leave our eldest son out with fear he may feel neglected. We constantly carry around a whole weight of guilt, guilty we can't do more for [redacted], guilty that we have less time for [redacted], guilty people are sending donations to fund equipment for our son, guilty of we go out for the day as hoping people don't think we are spending the fundraising money, the list goes on... it's like handing your life over. I wish I could literally swap places with you decision makers for 1 week and put your family and children in this exact same situation, just to experience what this feels like- this is real for us and although I still keep feeling that this bubbles going to burst and I'm going to go back to 'normal' life soon. It actually has got worse, as we once had hope for a treatment for our son and that hope is drifting away, please don't let it go, please keep my hope alive and give my son treatment and an opportunity for a future. If [redacted] does not get treatment and soon, he will continue to deteriorate and will require care 24/7 for life, he will be literally paralysed. Have you truly added the cost effectiveness of giving treatment against how much it will cost the Country in care, equipment, prof appointments, DLA, Carers Allowance, DFG etc? More drugs are coming through and being trialled, but access should be given NOW! Treat all the patients with the known approved drug NOW!! Make that difference NOW!! The price may be high at the moment but it will not remain this high forever as new drugs are on the way! If countries all over the world are approving this, 20 in the EU alone, why can't we?! With the help of social media, we see families and patients benefiting daily from this drug, it's making such a huge difference to their lives. Whilst this is amazing to see and quite rightly the individuals are able to access it, but imagine how that make us feel as parents? This is what you could be like son if you had this treatment but unfortunately you can't as we live in England. I dread the day I need to explain to him, but that day is fast approaching. It hurts.	s in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA. Section 3.3 of the FAD has been amended to emphasise the substantial effect of SMA on multiple members of the family. The company have made several attempts to better incorporate the

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			I represented my country in front of the queen at The Royal Windsor Horse Show when I was younger, I have never felt so let down by my own country and this health system. Shame on you if you don't make the right decision. Don't put a price on my child's life? Would you for your own child?!	cost of living with SMA, but the costs remain to be very uncertain (see section 3.19 of the FAD). This uncertainty will be addressed in the MAA.
83	**Web comments**	Carer 15 (parent)	From a family with a 4 month old daughter who has recently been diagnosed with SMA Type1 my comments here relate more to the drug availability not the report. That said, I do believe these comment should be treated with equal value. I have read the document and understand the biggest factor here is cost. To be fair, finances pretty much structure and control most things within society at this present time. However the treatment Nusinersen has given our family something money can't buy and that is a feeling called 'hope' Now I don't know if this treatment will help our daughter or not but we will always be grateful that she will be given the chance to try and make the most of this treatment and show signs of improvement. What really hurts us as a family is knowing that in a few months time another family just like us are going to receive devastating news in a hospital meeting room that their child has been tested positive for SMA type 1. What hurts even more is they potentially will not be given the chance to hold onto the 'hope' that we are currently hanging on to each day.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
84	**Web comments**	Carer 16 (parent)	My son [redacted] is currently receiving Spinraza at Gosh for type type 1c SMA. he was lucky enough to be included into the expanded access program for a select group of children. Since receiving his treatment we have watched the transformation of a seriously weakening child to a thriving boy who has gained significant progress in his motor function and	Thank you for your comment. The

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			health we are continually amazed by his progress. He starts pre school in the coming weeks an achievement we never thought possible. With the right support and treatment children just like [redacted] will live a happy more fulfilled lifes. Since Spinraza we are excited for his future no mater what it intails. I think every child deserves a chance like [redacted]. I think this treatment should be available to everyone suffering from SMA despite of cost. [redacted]	recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
85	**Web comments**	Carer 17 (parent)	We have been taking our 13-year-old son, who has Spinal Muscular Atrophy Type 3a, overseas for Nusinersen treatment since March 2017 (when he was age 11). He has now had 7 lifechanging treatments. 1. Previously, without treatment Our son's growth spurts accelerated degeneration. His condition had caused degeneration to the point where he fell at least 2 times a day & on some days multiple times. If he fell in the middle of the room, he would crawl and drag himself over to a chair to assist himself up to climb up furniture to stand - such as a chair. This was often unsuccessful in which case he required assistance to get up from a parent / carer. He had become increasingly reliant on his wheelchair to get around, especially outside. He had become reliant on his parent or a carer to assist with activities of daily living such as dressing, putting on his socks, shoes and splints. His father would have to carry him upstairs if he had become too tired to crawl up or down. He had bilateral pronated flat feet, pressure areas and experienced pain. Before treatment our son regularly fell and collapsed which often resulted in severe pain. He had several bad falls where he could not weight-bear requiring A&E treatment. He has had metatarsal fracture and soft tissue injuries over the years from falling that have caused him to have difficulty and pain weightbearing. The emotional impact of the condition was such that each bad fall resulted in him being petrified that he would NEVER walk	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients,

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			again. We were extremely concerned & anxious about our son having a bad fall that would result in a fracture. We had read about boys with SMA type 3 around our son's age that had sustained a fracture and after immobilisation never walked again. We feared and were anxious that if he lost the ability to walk and became wheelchair bound, with the exacerbation of SMA disease progression he would be at increased risk of more pressure areas, immobilisation leading to respiratory problems requiring Non-Invasive Ventilation, scoliosis, pneumonia, becoming bedbound and having swallowing problems. 2. Our observations following treatment Our son doesn't fall or collapse as he did before treatment. He can walk faster & further. His gait has improved & is much less 'waddling' we have video evidence. He now walks at least 1 mile a day. He uses his wheelchair less and less over time. He is able to walk further & faster with more stamina as he has continued treatment & does not fatigue as he did before treatment. He can cycle on the exercise bike, which was never a possibility, and this is getting better & faster with every treatment ' we have video evidence. Our son can now independently rise from the floor again & with each treatment he is becoming obviously better at this & stronger again we have video evidence. He is no longer reliant on his parent or a carer to assist with activities of daily living such as dressing, putting on his socks, shoes and splints. He can manage walking up and down stairs. After the loading doses his right foot developed an arch and he no longer develops pressure areas or pain. This has also enhanced his walking ability with a narrower base and less waddling gait. Nusinersen treatment has benefitted our son emotionally. He can feel he is becoming increasingly able and independent which is positively affecting his attitude to life. He is NO LONGER scared of losing ability and getting weaker. He is embracing life and is now developing without fear, he is becoming stronger, he has more stamina and he is developing and becoming MORE ABLE as he grows. He has a thirst for knowledge & life. He is exceptional in all subjects at school. He wants to study Law at Oxbridge. With treatment, our son will not face the future we feared. 3. Clinical evidence pre and following treatment In December 2015 when he was 10-years-old, before Nusinersen treatment, he • walked 301.5 metres in the 6-minute walk controlled test • weight 38kg • height 142cm. After 7 Nusinersen treatments, in June 2018, he • walked 350 metres in the 6-minute walk test • weight had increased to 42.3kg • height had increased to 154cm.	carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.

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			This 6-minute walk test result following treatment was contrary to our pre-treatment experience when our son's height and weight gains accelerated degeneration. Such a deterioration is confirmed by Montes et al (2010) confirm as the natural progression of untreated SMA Type 3. 4. Costs of Care I have been gathering my own evidence on the incremental benefit of Nusinersen to our son. Education Our son goes to our local mainstream selective school where he is excelling academically and he is extremely sociable & popular. Our local authority have given me the costing for him to attend the nearest school for physically & neurologically impaired children. Without Nusinersen treatment, and with the predicted physical degeneration, he would meet the entry criteria. • £22,800 per annum - transport costs • £21,269.26 per annum school placement (based on 2017/18 prices). • £44069.26 Total Community Care The 'lower care' community care costings I have received are: • £18 per hour day care, • £24 per hour night care, • £30 per hour Sunday & bank holidays. Total up to £161,856 per annum (taking into consideration 40 weeks term time) For 'complex care', costs are: • £38 per hour day care, • £45 per hour night care, • £54 per hour Sundays & bank holidays. Total up to £307,584 per annum. Other health related costs These include equipment and hospital costs including Outpatient Department appointments & patient admissions. All of these costs could be avoided if our son could receive Nusinersen treatment at home in England. 5. Our future 'our son, our family and us as parents and carers Our son could go on to be a high earning tax payer putting into the system rather than taking out. My beautiful, bright and fun child is at the centre of this and his future and quality of life has been completed disregarded with the decision not to approve Spinraza. Why is my child's life not important? SMA type 3a is a severe and debilitating disease without treatment. Nusinersen has transformed our son & our families' life. If Nusinersen is not recommended by NICE for SMA type 3a in England our family will have to break up leaving his brother, 2 sisters my husband and son's father behind in order for me to try and move abroad with our son so that he can access treatment. Our son loves his life in England. He enjoys school, has a great set of friends and a loving extended family surrounding him. He NEEDS Nusinersen treatment in order to live an independent life. With continued Nusinersen treatment our son can achieve his goals being independent with activities of daily living. He is now age 13 and he is becoming more confident & happier as he grows. With Nusinersen treatment he is NO LONGER TRAPPED in a degenerating body. Our son has a life & his future ahead of him as he deserves. Nusinersen has huge implications for our son's future and the future of our family. With continued Nusinersen treatment he can	

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			live an independent life, where I'm sure this exceptional student will have an exceptional career and be an absolute asset to our society. With Nusinersen treatment, his body is NOT degenerating but improving and he does NOT face a fearful future losing abilities and associated devastating sequalae & suffering due to SMA disease progression. To watch your child throughout their childhood increasingly struggle, suffer or be in pain as they grow is cruel & devastating. Our son's improved abilities have welcomingly led to decreased physical demands for us as carers. We are less anxious about his condition as he isn't falling and is generally doing so much better. With Nusinersen treatment our caring duties will continue to diminish. We can continue our careers and will not have to give them up to become full time carers for our son as we thought we would. Reduced caring responsibilities mean that family life has become easier and happier for all of us & of course most importantly for our son. With Nusinersen, disease progression has halted and we no longer have to watch our son continuously struggle as he once did, we are amazed at our son's response to treatment that has changed all of our lives and futures for the better. It is really difficult to articulate the profound effect this treatment has had on our family & our outlook for the future knowing that our son WILL NOT degenerate. My husband just started a new job in January 2018, he felt he could take on the new challenge. I too in January 2018 had a promotion. We wouldn't have taken on these new roles before treatment. 6. We desperately need NICE to recommend Nusinersen Without treatment our son will endure torture in the form of physical & mental suffering as SMA would rob him of his independence causing him to rely on a carer to assist with all activities of daily living 'including washing, dressing, toileting. There is no dignity in unnecessary degeneration that can be avoided with treatment. ALL of the SUFFERING can be avoided with continued Nusinersen treatment. We need our son to access Nusinersen treatment at home in England as soon as possible. As his SMA disease progression has halted & his abilities are improving, he will need to access other health services less over time. Yet without treatment, over time our son would require increasing Health & Social Care services. His health needs would become increasingly complex and costly to health and social care services as his abilities would degenerate and associated sequalae and suffering onset. All the available up to date evidence-based research demonstrates the efficacy of Nusinersen in all types of SMA. Nusinersen has been validated to be effective in SMA type 1, 2 & 3. Our son has SMA type 3a and we have our own video evidence, objective evidence from his local Physiotherapist & objective evidence from his UK specialist centre and Neurologist overseas that demonstrate his improvement with Nusinersen treatment. Please recommend Nusinersen for SMA types 3. This is a cost-effective treatment for the long term and lifechanging & life saving for the affected individuals and their families. We need NICE to recommend Nusinersen for SMA type 3a. Our son showed symptoms of low tone as an infant at 8 months assessed by a Health Visitor. Our son continued to develop slowly, falling frequently with many A&E attendances as a baby & young child. Our son didn't reach all his milestones but as he achieved the ability to walk very late he was classified as SMA type 3a on diagnosis. Before our son started Nusinersen treatment he presented very similarly to a stronger Type 2 SMA individual. There is such a huge spectrum within each type of SMA. In a scenario where SMA type 3a individuals like my son were denied Nusinersen treatment he would lose the ability to walk and physically degenerate to become like a SMA type 2 or SMA type 1 individual. Whereas SMA type 1 and 2 patients with treatment will get stronger and may achieve the ability to walk. All SMA type 1, 2 & 3 affected individuals deserve access to Nusinersen treatment. Any decision not to give treatment to type 1, 2 and 3 SMA would be perverse and discriminatory to only recommend for individual types, that is not a broad recommendation for type 1, 2 & 3. We are regular hard- working citizens who want our child's suffering and loss of function and ability to end now with ongoing treatment at home. Our son's positive response to Nusinersen treatment has had had a huge impact on our entire family. Our home is a happier place where we look forward to all of our futures and are not scared of him	

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			growing and deteriorating. In fact, we look forward what each new day brings and we are excited about what he can NOW DO. Please help my son by recommending Nusinersen SMA including SMA type 3a.	
86	**Web comments**	Carer 18	It's is crucial that nice listen to the success stories for spinraza! This drug is saving life's and improving quality of life! Please see below Please find below details of [redacted] spinraza success... [redacted] had numerous hospital admissions multiple times each year and this had been since birth, since starting spinraza she's been admission free. We have been able to reduce her bipap pressures which were stuck on 18/10 for over a year she is now on 16/6 which has never been possible. She can now feed her self and enjoys more of a variety of foods (previously purée foods or peg feeds) her head control and arm control has increased massively she can now put a fork to her mouth and is learning how to use a knife and fork Her trunk is her greatly increased she can now lean and is less floppy. She has previously had a neck brace for her head flopping especially when in the car she no longer requires this. [redacted] quality of life has increased dramatically, she can play more with friends, hair and teeth brushing is easier and she is able to help, her confidence has increased at school playing with piers. We are so happy that she has gained on her chop test and the results have been outstanding. We were informed that [redacted] may not find any benefits with spinraza due to her age, we was happy to try and maybe maintain her abilities. I feel [redacted] has changed so much for the better and this has had a huge impact on the whole family. We regularly get people stating how strong [redacted] is looking and that she is doing new things at school. This drug is life changing for families as well as the child. We hope that other families are given the same chance as [redacted] [redacted] has been given and improve their health and quality of life. If you require any further assistance please call me on [redacted] Kind regards [redacted]	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
87	**Web comments**	Patient 1	Though I have already sent this by email to the project lead, I am submitting it here to as I have no confirmation that my email was received. The comment box is not big enough for my complete submission, so please use the multiple comments as one piece chopped into box-friendly parcels. To whom it may concern at NICE I was dismayed but unsurprised by your proposal not to recommend the use of Nusinersen in adults with Spinal Muscular Atrophy (SMA), given the need for more studies to be undertaken to demonstrate its efficacy. I was shocked by your proposal not to recommend the use of Nusinersen in children with Spinal Muscular Atrophy (SMA),	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into

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			given the body of evidence that shows the treatment has clear clinical benefits. Looking deeper into your decision making process, I remain shocked. Please find below a summary of my thoughts and some questions I would be keen to see answered. I look forward to your reply and would be happy to meet with you to discuss this further. Yours faithfully [redacted] Adult with SMA type II Question: By what processes does NICE take account of its duties as a public authority to act in a manner consistent with human rights? These children, like all children, have a right to life. I draw your attention to the UN Universal Declaration of Human Rights, Article 3:“Everyone has the right to life, liberty and security of person“.(UN, 1948) And also to the UN Convention on the Rights of Persons with Disabilities, Article 10: “Right to life States Parties reaffirm that every human being has the inherent right to life and shall take all necessary measures to ensure its effective enjoyment by persons with disabilities on an equal basis with others. ” (UN, 2006) These aspirations are realised through the Human Rights Act 1998, Article 2: “Right to life Everyone’s right to life shall be protected by law. No one shall be deprived of his life intentionally save in the execution of a sentence of a court following his conviction of a crime for which this penalty is provided by law.”(Legislation.gov, 2018) Publicly available information from the Equality and Human Rights Commission states “Public authorities should also consider your right to life when making decisions that might put you in danger or that affect your life expectancy.”(EHRC, 2018) NICE recommendations are used to influence real-world decisions and patient pathways; NICE has a duty under the HRA to act in a way that protects life. Nusinersen has been shown to protect the life of children with SMA. It is the first and only treatment of its kind designed to do so. Decisions which impact patient access to this drug affect these patients right to life. Despite this, the right to life does not appear to be not explicitly mentioned in NICE's consultation. If NICE were to not recommend a life-extending treatment without sufficient justification, NICE could be found to be not acting in accordance with the HRA. The NICE website does show that NICE is aware of its duties under the HRA, though offers little detail as to how it ensures it discharges them.	account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA. NICE’s decision making processes are compliant with relevant anti-discrimination legislation. Legislation on human rights, discrimination and equality requires that patients are not denied access, or have different or restricted access, to NHS care because of their race, disability, age, sex/gender, sexual

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			From NICE'S EQUALITY OBJECTIVES AND EQUALITY PROGRAMME 2016-2020 (NICE, 2016) "The Human Rights Act 1998 8. When public authorities such as NICE carry out 'functions of a public nature', they have a duty under the Human Rights Act 1998 not to act incompatibly with rights under the European Convention for the Protection of Fundamental Rights and Freedoms. The Equality Act's public sector equality duty uses the same definition of functions of a public nature as the Human Rights Act 1998. The Human Rights Act places responsibility for ownership of human rights matters on every public body and employee and requires active consideration of whether decisions have any implications for human rights." ... "NICE's compliance with the Human Rights Act 35. NICE achieves compliance with human rights requirements primarily through: • a robust procedural framework for developing guidance • an equality analysis process that also looks at the situation of groups in addition to those who share the characteristics protected under the Equality Act • asking advisory bodies to satisfy themselves that their decision making procedure is fair and transparent, that decisions do not discriminate against a group that is not a legally protected group, and, if they do, whether that discrimination is legitimate "obtaining legal advice when an issue arises that could potentially lead to challenge." Despite these assertions, the procedural frameworks (NICE, 2017, 2017, 2018) underpinning the Nusinersen decision do not appear to discuss how to make decisions which respect every individual's human rights, including right to life. Within the Nusinersen consultation document (NICE, 2018), there appears to be no explicit mention of human rights or right to life. In all human rights discussions, the needs of the individual must be weighed against the needs of collective. NICE's approach to this is to calculate the cost relative to the benefit; incremental cost-effectiveness ratios (ICERs) per quality adjusted life year (QALY). A very high cost treatment which did not have a significant effect on health related quality of life (HRQL) would have a large ICER per QALY. The inverse is also true. Funding very high cost treatments which have very small benefits is unsustainable, and so the wider economic picture must be balanced against the needs of an individual or group of people. Both must be carefully assessed and considered in a robust decision making process. In this case, we are establishing whether it would be financially sustainable for the NHS to give children with SMA access to the only life-protecting treatment of its kind. NICE's SOCIAL VALUE JUDGEMENTS, Principles for the development of NICE guidance, Second edition (NICE, 2008) states: "NICE has never identified an ICER above which interventions should not be recommended and below which they should. However, in general, interventions with an ICER of less than £20,000 per QALY gained are considered to be cost effective."	orientation, religion, beliefs, or socioeconomic or other status For further details see NICE's Equality objectives and equality programme 2016-2020 The maximum acceptable ICER is £20,000-£30,000 per QALY, as described in section 5.8.10 of the NICE's guide to the methods of technology appraisal. Section 5.3 of NICE's methods guide (link above) reports how health effects should be measured and valued. Following consultation the company have described how they have valued health effects in section 2.4 of the addendum to their submission dated February 2019. The

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			Question: What is the evidence based rationale behind this figure of £20,000 per QALY being used as a general guideline for cost-effectiveness? Question: Does this figure change with inflation? Does it change according to the financial realities of the NHS at the time of decision making? Given that the cost-effectiveness of Nusinersen is assessed through the ICER per QALY measure, it is important to ensure that the QALY measure is reflective of the individual experience of these patients and those around them. However, there does not seem to be a consistent definition of a QALY used across all NICE decision making. Measurement of quality of life of very young children has been pointed out in the Committee papers (NICE, 2018) as extremely difficult. Similarly, it was noted that the PedsQL may not be an appropriate tool to measure outcomes which matter to school-age children with SMA. The approach to collecting data about health related quality of life of these children focuses on adverse events (such as respiratory infections), hospitalisations, motor milestones (rolling, sitting, lifting objects...), and interviews with a small number of clinical practitioners. There is no publicly available summary of the interviews with the clinical practitioners. Though it is important to maintain doctor-patient confidentiality and to allow the clinical practitioners to feel they can speak freely without fear of public/media misinterpretation, the lack of transparency feels disconcerting. Request: NICE seek the permission of the clinicians to publish a bullet pointed summary of the key points. There appears to be no explanation of how the clinicians views and measured outcomes were converted to a numerical value; the QALY. Given the importance of the QALY to the ICER per QALY measure, and thus to whether or not children will be treated with Nusinersen, it is important that this calculation is transparent. Question: By what process was the information gathered converted into a QALY? NICE has compared Nusinersen against best case usual care (henceforth best possible care) to give a value for the ICER. This neglects to reflect the reality of the situation for children with SMA and their families. Many of the parent submissions talked of the difficulties associated with lifting a growing child, lack of sleep, getting the right equipment and making adaptations to the house. Best possible care would include steps to address these issues being taken by non-NHS bodies acting appropriately in a timely manner, providing and advising on equipment, housing, social care, respite and so on. The submissions you received reflect that this does not always happen smoothly. Best possible care is not the same as currently available care. Similarly, best possible care is not always delivered by the medical team around the child. Within the company submission (Figure 34 and surrounding discussion), it is acknowledged that the UK standard of care in practice is not the same as that in other countries, highlighted by data from Italy. The UK does not presently deliver the best standard of care, which has a	company also provided a summary of clinician interviews. This was considered an acceptable level of detail by the ERG and committee All potentially relevant comparators are identified in the scope (see section 2.24-2.2.5 in the methods manual; link above), which is typically subject to a public consultation. Best supportive care (BSC) is typically chosen to describe the care a person typically receives in the NHS for an indication. It is usual for BSC to be variable for situations in which NICE considers a new treatment. In these situations, in order for NICE to better

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			significant impact on patient survival. This must be addressed outside of the present discussion. Given that best possible care is not uniformly experienced by children with SMA in the UK at present, it does not seem logical to use it as a direct comparator when looking at Nusinersen. The “Green Book”from HM Treasury (HM Treasury, 2018) sets out a suggested process by which options of how to spend public money can be appraised. It recommends looking at an option compared to business as usual (BAU). In this situation, that would be a model of care which takes into account gaps in provision and waiting times for equipment, advice, and treatment, and the effects this has on children with SMA and their families. Request: NICE produce a BAU model of care to use as comparator to Nusinersen. The decision on whether or not to recommend Nusinersen and any medical technology must happen through a process which is fair, transparent, and uniformly applied. I request that NICE not only review the decision to not recommend Nusinersen, but also review the process by which such decisions are made so to make it clearer how NICE carries out its duties. A final word on quality of life The submissions to NICE reflected the downsides of having SMA. However, it also seems important to mention that when health is stable, and the correct support is available, a good quality of life can be achieved. Here are some examples from adults with SMA: [redacted] (me): - 3 highlights from the past year: Seeing the Killers play live at the O2, meeting some of my heroes at London Comic-con in full cosplay with 2 of my best friends, meeting [redacted] - the highlight of the past month: Helping put together a last-minute surprise celebration for a family event complete with gold-edged invitations, and the looks on my rellys’ faces as we laughed and ate and drank altogether for the first time in 4 years. - something you're looking forward to?: Finishing my Physics degree and possibly starting a Masters [redacted]: 3 highlights from the past year: “- visiting Egypt and my 4th continent. Being featured on the BBC about successful people. Launching a marketing agency.” Highlight of the past month: “- driving again after 9 months” Something you're looking forward to: “- my next goal in excited to achieve is delivering a Ted talk” [redacted]: “Passed Year - 1. A few amazing concerts, Celine Dion, Steps and Taylor Swift at Wembley... 2. Taking on Coventry City Council regarding a potential massive cut to my care package, featuring in the Guardian and being on my local radio, my fight continues still ... 3. Finding out my daughter is pregnant, I’m to be a Nanny! Last month - the news I’m having a Grandson	understand how the new treatment compares against usual care, companies need to determine a best estimate of what is usual care. The committee acknowledged that the standard of care in the UK is constantly evolving (see section 3.19 of the FAD with respect to estimating current treatment costs) which contributed to the uncertainty in estimating overall healthcare costs. NICE regularly reviews its methods.

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			Future - to win my care battle and to guide and influence my grandson to be a true gentleman and achieve his dreams... which he will as he has a strong feisty Nanny by his side! [redacted]: “3 highlights from my year - being brave enough to give up work and spend more time with my family and my kids growing up. - having a lot more energy for the people that I love and doing things together not just 30 days a year. - Started Painting with my mouth, one day I would like to be able to do it for a living. Highlight of the last month - (probably more like the last 3 months) it's warm enough for me to walk the dog without hands stopping working. I bloody love the sun! Future - I would like to drive again, I used to drive 700-1000 miles a week commuting to London and living a life, had to give that up because I got too weak to do with confidence any more. Really need to get something to enable me to do that. [redacted] “-3 things you love doing/are proud of Career Positivity Home -3 things you wish you could still do that you used to Feed myself Wash myself Hold my phone to my ear -3 things you’re scared of losing the ability to do Work Drive Socialise [redacted] “3 things you love doing/are proud of - Enjoying a social life, theatre, cinema, meeting up with friends and watching my granddaughter grow up. Having a (reasonably!) active, alert mind which can cope with what life throws at it, mentally at least. The fact that I have spent a good deal of my life working and living to the best of my ability despite SMA Type 3 doing its best to make it very difficult. 3 things you used to do that you wish you could still do Drive Wash myself Walk 3 things you're scared of losing the ability to do	

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			Speak Write Laugh References: UN (1948) The Universal Declaration of Human Rights. Available at http://www.un.org/en/universal-declaration-human-rights/ (Accessed 1 September 2018). UN (2006) Convention on the Rights of Persons with Disabilities (CRPD), Article 10 - Right to life. Available at https://www.un.org/development/desa/disabilities/convention-on-the-rights-of-persons-with-disabilities/article-10-right-to-life.html (Accessed 1 September 2018). Legislation.gov (2018) Human Rights Act 1998. Available at https://www.legislation.gov.uk/ukpga/1998/42/schedule/1 (Accessed 1 September 2018). Equality and Human Rights Commission (2018) Article 2: Right to life. Available at https://www.equalityhumanrights.com/en/human-rights-act/article-2-right-life (Accessed 1 September 2018). NICE (2016) NICE'S EQUALITY OBJECTIVES AND EQUALITY PROGRAMME 2016-2020. Available at https://www.nice.org.uk/Media/Default/About/Who-we-are/Policies-and-procedures/NICE-equality-scheme/equality-objectives-and-equality-programme-16.pdf (Accessed 1 September 2018). NICE (2017) Medical technologies evaluation programme process guide [PMG34]. Available at https://www.nice.org.uk/process/pmg34/chapter/introduction (Accessed 1 September 2018). NICE (2017) Medical technologies evaluation programme methods guide [PMG33]. Available at https://www.nice.org.uk/process/pmg33/chapter/introduction (Accessed 1 September 2018). NICE (2018) Guide to the processes of technology appraisal [PMG19]. Available at https://www.nice.org.uk/process/pmg19/chapter/acknowledgements (Accessed 1 September 2018). NICE (2018) Appraisal consultation document, Nusinersen for treating spinal muscular atrophy. Available at https://www.nice.org.uk/guidance/GID-TA10281/documents/appraisal-consultation-document (Accessed 1 September 2018). NICE (2008) SOCIAL VALUE JUDGEMENTS, Principles for the development of NICE guidance, Second edition. Available at https://www.nice.org.uk/media/default/about/what-we-do/research-and-development/social-value-judgements-principles-for-the-development-of-nice-guidance.pdf (Accessed 1 September 2018). NICE (2018) Single Technology Appraisal, Nusinersen for treating spinal muscular atrophy [ID1069], Committee papers. Available at https://www.nice.org.uk/guidance/gid-ta10281/documents/committee-papers (Accessed 1 September 2018). HM Treasury (2018) THE GREEN BOOK, CENTRAL GOVERNMENT GUIDANCE ON APPRAISAL AND EVALUATION.	

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			Available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/685903/The_Green_Book.pdf (Accessed 1 September 2018).	
88	**Web comments**	Family member 1 (Grandmother and helper of a child with SMA Type 2)	I am concerned that the NICE appraisal has major shortcomings. A letter written last month to NICE by Francesco Muntoni, Prof of Paediatric Neurology and NIHR Senior Investigator, UCL Great Ormond Street and Ros Quinlivan, Consultant in Neuromuscular Disorders, Medical Research Centre, National Hospital for Neurology & Neurosurgery and endorsed by clinicians across the country plus the three major SMA research/support charities in UK and Muscular Dystrophy UK asserted that the regular commissioning route is too inflexible for the appraisal of a drug such as nusinersen, and that it fails to provide an effective mechanism to respond to the needs of subgroups of children with devastating conditions such as SMA. The full letter is at http://www.smasupportuk.org.uk/files/files/Research/Nusinersen%20letter%20to%20NICE%2020_8_18.pdf Prof Muntoni and Ms Ros Quinlivan also criticise the time taken in producing the NICE appraisal. Section 3.1 I strongly support the patient experts' view that the classification system does not reflect the full extent of the condition within each Type. By way of example, I refer to a child classified as Type 2 merely because he was able to sit unsupported at 6 months; but he was never able to pull himself into a sitting position, let alone right himself when he flopped. Within a few months the child's ability to sit unsupported was lost. He has never crawled, receives nutrition and fluids by PEG and needs non-invasive lung support when at rest as well as at bedtime. He cannot stand; for mobility, he must be carried to his powered wheelchair. There are children of a similar age with Type 2 but at the other end of the scale whose symptoms are far less severe. Section 3.2 The emotional, physical and financial stresses on a SMA child's parents are enormous - on his mother as main carer, on his father as breadwinner, juggling between dealing with a responsible work position and helping at home as second carer. Referring to a child with SMA Type 2, the near-death episodes with respiratory problems necessitating emergency admissions, each of several weeks, have been particularly telling on both parents with the father taking holiday leave, unpaid leave and, on occasions, sick leave to be with the child in hospital. The child's teenage brother has also suffered owing to separations from his immediate family while his parents resided in hospital accommodation to be with the child. Nusinersen would undoubtedly have alleviated so much of this. Without nusinersen, the child's and the immediate family's lives will continue to be on a knife-edge with fear of the progression of the disease, fear of hospital emergencies, fear of ever diminishing mobility, fear of early loss of life. Section 3.18 Evidence shows that nusinersen halts the degenerative process of SMA and, when administered soon enough, to improve a range of outcomes important to the patient, especially including respiratory and swallowing problems. It is established that current treatments merely manage symptoms. When weighing up the cost effectiveness, we should consider the holistic cost of current treatments and all knock-on effects on	Thank you for your comments. Following extensive discussion at scoping, it was agreed that this topic is appropriate for consideration as an STA. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the

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			the patient, his parents and siblings. Almost every problem encountered by SMA patients and family is specialised and 'specialised' inevitably means great expense, either to them or to the state, whether medical, mobilising, social opportunities, mental health, or merely dealing with everyday functioning. By way of example, a child with SMA Type 2, from the age of 2yrs and over a span of 3 years, endured 8 emergency hospital admissions for serious respiratory problems entailing stays in paediatric intensive care/high dependency of up to 6 weeks on each occasion. At least three (maybe more) of these emergencies necessitated paramedics/ambulance service. There have been, and still are, routine overnight studies, PEG operations, countless outpatient appointments with consultants, respiratory nurses, physios, nutritionists, GPs, OTs, and others; countless home visits by physios, respiratory nurses, NG nurses, PEG nurses, OTs, others; countless prescription medicines; a wealth of specialised disability and mobility equipment, specialised respiratory and physio machines, regular deliveries of feeding and respiratory supplies. The family home was modified to make it wheelchair friendly a local government grant was allocated; the remaining sum needed fell to the family to find. The mainstream pre-school playgroup which the child attended was allocated a grant for wheelchair access/accessible toilet and funding was provided for a one-to-one constant carer whilst he was there. The same carer is now with him constantly at mainstream school the school obtained funding for; also to create accessibility, in particular an accessible toilet/washroom with hoist. Motability was awarded to fund a large family vehicle to transport the child and his powered chair; there is also Parent/Carer Allowance and Funded Respite Care (when details have been finalised) If nusinersen is not administered, the child at approximately 10years old, will need an operation to insert rods in his spine to combat scoliosis; every few months he will return to have the rods lengthened to keep up with growth. When he has stopped growing, there will be a major operation. And so it goes on. Current treatments and endless 'knock-on' problems, not only for the patient but also for the immediate family, entail huge expenses for life 'I don't question that they'd be less than the cost of nusinersen but they could be set against the treatment cost with reasonable effect. If we suppose that the child had been administered nusinersen on diagnosis at 18months, and the progress of SMA had been halted, it could be expected that the best part of the expense of current treatments and 'knock-on' effects would have been eliminated. Section 3.19 In my opinion, NICE's preliminary recommendations discriminate against children and adults with disabilities caused by SMA. Nusinersen is an available disease-modifying treatment and if this is not approved for funding by NHS, those people with SMA will be committed to face progressive muscle loss, furthering their disabilities and huge difficulties in life, resulting in a life shortening outcome. As mentioned before, the letter to NICE from Prof Francesco Muntoni, Ros Quinlivan and company, contains criticism of the length of time taken to produce the appraisal. This could also be considered discriminatory; urgent disease-modifying treatment is needed now, not later, to halt the progress of SMA. Again, I refer to a 5yr old child with Type 2 who, without availability of nusinersen on the NHS, will need scoliosis corrective	context of a MAA. Section 3.3 and section 3.19 of the FAD have been amended to emphasise the impact on family members and underestimated costs of living with SMA. The appraisal process was delayed for several reasons including that the company wished to submit further evidence and because the company have been in discussion with NHS England to negotiate a commercial agreement. NICE's decision making processes are compliant with relevant anti-discrimination legislation. Legislation on human rights, discrimination and equality

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			surgery within the next few years. Lumbar puncture procedures are more difficult after such surgery. It seems discriminatory, not only to allow progressive disability, but also to jeopardise the possibility of being treated with nusinersen should it become approved. More importantly, without nusinersen, parents of babies born with Type 1 SMA face the prospect of death of their children before reaching their 2nd birthday. This, surely, is discrimination. NICE's preliminary recommendation would have a most adverse effect on those suffering from SMA . The children, in general, are noted for being bright and happy with a huge zest for life and destined to play positive parts in our community. If their disabilities could be halted or lessened, and they could live longer, they would play an even greater part.	requires that patients are not denied access, or have different or restricted access, to NHS care because of their disability. The committee documented their consideration of equality issues in the Equality Impact Assessment form that is published as part of Final Guidance.
89	**Web comments**	Family member 2 (Grandmother and helper of a child with SMA Type 2)	I am aware of children with type 2/3 SMA who have been receiving treatment with Spinraza for 18 months in the USA. Their life experience and ability to function physically have been transformed by this treatment. Intellectual assessment have placed some children at the 96th percentile and they regularly exceed educational expectations. Without Spinraza they would be unable to access school and would probably no longer be with us. Having read the NICE consultation document I find it very worrying that NICE does not acknowledge the research that led to Spinraza being provided for children with ALL forms of SMA across the globe. Cost effectiveness seems to be NICE's main concern. If countries like Greece with all of its financial problems can find the money to fund Spinraza for all SMA diagnosed children, then I believe the UK has a moral duty to follow suit. Other countries such as Australia, Spain and the USA (and many more) have accepted the transformative effect that Spinraza has had on children with all forms of SMA and their families. I am at a loss to understand why NICE should interpret research data in such a negative way when so many other countries are being so positive about the effects of Spinraza. Families want to live and work (and go to school) in their home country of the UK (specifically England). I urge NICE to reconsider the recommendations in its consultation document and to recommend that Spinraza should be made available on the NHS for children with ALL forms of SMA.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA.

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				Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
90	**Web comments**	Family member 3 (Granny)	My grand-daughter has been diagnosed with Spinal Muscular Atrophy Type 2/3. Which, as you know, is a rare, inherited muscle -wasting disease. If untreated, she will, by the time she is about 10, be in a wheelchair, unable to move, breathe or swallow without aids, and be doubly incontinent, but still have a normal life expectancy, this will be such a waste of life and devastating for our family to watch her deterioration month by month and be powerless to do anything to prevent it. Spinraza/Nurinsen has been welcomed and funded by countries across the world including poorer countries such as Greece and Portugal who have been able to broker a deal with Biogen would are keen to come to a favourable financial arrangement with the NHS in England. I feel that the NICE report is flawed in many ways: A totally negative slant has been put on all of the evidence; It says that there is insufficient evidence of success while at the same time stating that the drug 'provided a substantial clinical benefit' and 'statistically significant improvement in motor function'; they stated that it was difficult to assess as there had been no deaths!; and that it would not be 'fair to people of all ages'! SMA is not fair. Neither is it fair to all children under 18 with SMA who, through no fault of their own, have developed this condition and have been refused treatment when other people with self-inflicted conditions such as obesity, drug and smoking related diseases etc are being treated with drugs agreed by NICE and paid for by the NHS. There are no other options other than Spinraza for my grand-daughter and others like her. Please, please agree to fund Spinraza for all under 18s in England.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
91	**Web comments**	Family member 3 (Dad)	I find the decision regarding the denial Nusinersen to people suffering SMA extremely disappointing. I feel that the evidence has not been fully appreciated and applied to real life cases; particularly to SMA type 3. The clinical evidence is compelling, conclusive and significant enough to demonstrate that the this drug has a marked effect on SMA type 3 in proving improved strength. The drug's genetic design is structured around splicing SMN 2, which SMA Type 3 people have more than other	Thank you for your comment. The recommendation

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			many other types of SMA (1&2). If Nusinersen was given to my 4yr old, SMA type 3, little girl, [redacted],it would allow her to gain the strength for independent living. As a type 3 she is a breath away from having the strength to toilet independently and move around just that little bit better; enough to afford an independent life. The promise of an independent life. She may never run for a bus, but she would be able to hold functionality to a point of independence. The cost benefits can be seen when we determine the high levels of intervention (operations and 24hr support) to a disease that takes away strength verses an independent life of an SMA type 3 with Nusinersen. I do not believe the evidence has been fully evaluated against specific SMA type profiles and the potential benefits this drug would deliver to a SMA type 3 child. The efficacy of this drug is beyond doubt with many countries in the world looking to safeguard their citizens with Nusinersen. The drug has virtually no ill effects whilst delivery increasing in strength across the range of indices. moreover, patients have been shown to continually improve their strength for as long as they are receiving the drug. As such, holding the view that the drug should be denied to people because of a lack of long term evidence is poorly constructed excuse for not releasing the drug to people that desperately need intervention. The UK is the 5th richest country on the planet and with other poorer country's finding arrangements with Biogen, i find it difficult to believe it is cost prohibitive. We have an NHS to provide health care and as normal citizens we pay into this system all our lives and have no other options to access this form of treatment, our little girl is in effect being sentenced to a long, slow, suffering demise. All of her life opportunities will be utterly spent whilst all along this drug can transform her world. I would urge NICE to reconsider; with particular focus on case by case access for those that the drug would allow for an independent life.	s in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
92	**Web comments**	NHS Professional 1 (Consultant Paediatric Neurologist with a Specialty Interest in Neuromuscular Disorders. Visiting Professor Chester University)	Dear Colleagues Re; Nusinersen treatment for SMA patients [ID1069] As a clinician involved in the care and translational research of children with a devastating neuromuscular disease, spinal muscular atrophy (SMA), I would like to express my deep disappointment in this treatment not being funded or given a positive outcome following the consultation. Severely affected children with SMA1 (who never acquire sitting position and who typically die at a mean age of 9 months of life) are now being offered a therapy that – especially if initiated close to the onset of disease- can substantially improve their motor function as well as respiratory function, feeding and life expectancy. This treatment allows a proportion of affected children the ability to acquire the sitting position and in some cases to stand. This current treatment is only one of many being developed and in the pipeline, including gene therapy, for this condition. In my personal practice we have a number of children receiving Nusinersen (N=7) and in all of these children, we have seen significant improvements in their abilities and quality of life. All these children received the Nusinersen later than those who experienced the best scores in the studies, as diagnoses were not made early, however in all there have been improvements. This may be less fatigue and ability to hold head up; one girl who is already 6 years but received the Nusinersen was very weak, but since the treatment has improved with motor control and now has a stronger voice and has not needed hospital	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients,

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			treatment at all in between her doses. For another child who was in ITU most of her life, since starting Nusinersen, has been at home in between her injections (which are 4 monthly) – she has not been this stable since she was born. I reviewed one of my patients last week, she is almost 2 years old (23 months) – she is now sitting independently, driving her own wheelchair, eats normally (No PEG tube) and does not need ventilation and each assessment is stronger and stronger. She started her injections at 8 months of age (so still relatively late compared to the study but still making huge progress). All these families are grateful for the extra time they have with their child but also the quality of time they have as they are stronger and more energetic. They are happy and are enjoying life. Whilst we do not know the long term outcomes of these children, neither do we for other such expensive treatments and cancer treatments. For those who are stronger with type 2 and 3 SMA, there may even be more strength achieved and less hospitalisation required which would potentially offset some of the cost from the type 1 SMA patient's requirements. There are many advances being made in the treatment of these rare conditions and at present this has been welcomed by the communities and it is encouraging to see our colleagues in America and Canada as well as the other European countries all funding this treatment, however the UK, whilst our children take part in the trails do not have access to the drug. As we become more insular and exit Europe, the pharmaceutical companies will realise the UK and NHS England will not fund the drugs once they are licenced. As a result they will begin to remove the funding, that we rely on, for research and the UK will see further deprivation in its healthcare as a result of tohis. I understand that these drugs are expensive and that there needs to be consideration for the ongoing costs, however all orphan drugs are expensive and for these rare diseases, the monies need to be reinvested to improve on the products and make them more effective. As a managed access programme (MAP) as in other drugs that we use, clinicians would be responsible for monitoring the effectiveness and benefit from the drug and as responsible clinicians we would not be continuing a drug that is not of benefit and at present think carefully when dealing with such children regarding the level care needed and benefit as well as best interest for that child. I hope that NICE and NHS England will re-consider its decision.	carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
93	**Web comments**	NHS Professional 2 ([redacted] Consultant Paediatric Neurologist with a Specialty Interest in Neuromuscular Disorders)	As a clinician involved in the care and translational research of children with a devastating neuromuscular disease, spinal muscular atrophy (SMA), I would like to express my deep disappointment in this treatment not being funded or given a positive outcome following the consultation. Severely affected children with SMA1 (who never acquire sitting position and who typically die at a mean age of 9 months of life) are now being offered a therapy that – especially if initiated close to the onset of disease- can substantially improve their motor function as well as respiratory function, feeding and life expectancy. This treatment allows a proportion of affected children the ability to acquire the sitting position and in some cases to stand. This current treatment is only one of many being developed and in the pipeline, including gene therapy, for this condition. In my personal practice we have a number of children receiving Nusinersen (N=7) and in all of these children, we have seen significant improvements in their abilities and quality of life. All these children received the Nusinersen later than those who experienced the best scores in the studies, as diagnoses were not made early, however in all there have been improvements. This may be less fatigue and ability to hold head up; one girl who is already 6 years but received the Nusinersen was very weak, but since the treatment has improved with motor control and now has a stronger voice and has not needed hospital treatment at all in between her doses. For another child who was in ITU most of her life, since starting Nusinersen, has been at home in between her injections (which are 4 monthly) – she has not been this stable since she was born. I reviewed one of my patients last week, she is almost 2 years old (23 months) – she is now sitting independently, driving her	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts

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			own wheelchair, eats normally (No PEG tube) and does not need ventilation and each assessment is stronger and stronger. She started her injections at 8 months of age (so still relatively late compared to the study but still making huge progress). All these families are grateful for the extra time they have with their child but also the quality of time they have as they are stronger and more energetic. They are happy and are enjoying life. Whilst we do not know the long term outcomes of these children, neither do we for other such expensive treatments and cancer treatments. For those who are stronger with type 2 and 3 SMA, there may even be more strength achieved and less hospitalisation required which would potentially offset some of the cost from the type 1 SMA patient's requirements. T here are many advances being made in the treatment of these rare conditions and at present this has been welcomed by the communities and it is encouraging to see our colleagues in America and Canada as well as the other European countries all funding this treatment, however the UK, whilst our children take part in the trails do not have access to the drug. As we become more insular and exit Europe, the pharmaceutical companies will realise the UK and NHS England will not fund the drugs once they are licenced. As a result they will begin to remove the funding, that we rely on, for research and the UK will see further deprivation in its healthcare as a result of this. I understand that these drugs are expensive and that there needs to be consideration for the ongoing costs, however all orphan drugs are expensive and for these rare diseases, the monies need to be reinvested to improve on the products and make them more effective. As a managed access programme (MAP) as in other drugs that we use, clinicians would be responsible for monitoring the effectiveness and benefit from the drug and as responsible clinicians we would not be continuing a drug that is not of benefit and at present think carefully when dealing with such children regarding the level care needed and benefit as well as best interest for that child. I hope that NICE and NHS England will re-consider its decision.	alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
94	**Web comments**	NHS Professional 3 (Consultant Paediatric neurologist)	The outcome of the NICE appraisal process is very disappointing. Other European countries have accepted the evidence provided that supports the benefits of nusinersen treatment for SMA in terms of promoting quality of life and preventing/ delaying respiratory failure. This is a lethal condition for which there is no other treatment, any child now born with this condition in England will develop respiratory failure and either require long term ventilation or die in early infancy. An urgent re-appraisal is therefore necessary to determine how those born with this devastating condition can access treatment within the NHS. The treatment is most likely to be beneficial if staretd within the earliest stages of symptoms and therefore any delay in providing treatment disadvantages those with this devsatating condition. It seems to me to be entirely unethical not to be providing this potentially life transforming treatment.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed

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				MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA. Furthermore, section 3.10 of the FAD now addresses early administration of nusinersen.
95	**Web comments**	NHS Professional 4 (Senior paediatric physiotherapist)	As a community physiotherapist I have had the experience in being part of a families devastating journey with a baby who died of Type 1 SMA before Nusinersen was available and am now involved with a family who are undergoing an entirely different experience with a type 1 baby who is receiving Nusinersen. Her progress has been remarkable she has gone from a floppy baby unable to interact due to no head control or active movement of limbs to a child that can sit independently after 12 months of treatment. She is able to play, feed herself, drive a motorized wheelchair and is a delight to all around her. She is thoroughly enjoying life and it is Nusinersen that has made the difference. There is no alternative treatment available and I am devastated to think that the next baby with SMA that is referred to me will not have this chance. I cannot imagine how I will be able to explain to parents that the NHS of which I am a proud member has made such a decision based on finance alone. I implore you to work with Biogen to reach a financial agreement so that this treatment can be offered to all.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic

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				and types 1, 2, and 3 SMA in the context of a MAA.
96	**Web comments**	NHS Professional 5 (retired GP - occasionally working as a locum)	Although I appreciate the comments in relation to a population of SMA sufferers, you cannot get away from the life-changing benefits to some. It must be possible to trial this for all sufferers and then look at who benefits. Even arresting this disease is a benefit, improving it is a miracle. We routinely spend this sort of money on other treatments and regimes.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
97	**Web comments**	NHS Professional 6 (Consultant paediatric Neurologist)	In an ideal world with all the available resources it would be wonderful to have the treatment with Nusinersen available for all children with SMA except type 0. Short of that, in my experience the ones with short disease duration respond the best. If we need to prioritise subgroups that will benefit the most then I would recommend the following: 1) SMA type 1- with disease duration <12 weeks. This is because this subgroup response is better compared to those with longer disease duration and there is risk of prolonging difficulties for some of the severely affected children. 2) all pre-symptomatically diagnosed siblings 3) All Type 2 SMA with disease duration less than a year	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed.

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				The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA. The responses to NICE's specific questions on clinically distinct subgroups fed into a workshop conducted by NICE to discuss these issues with clinical and patient experts. Furthermore, section 3.10 of the FAD now addresses early administration of nusinersen.

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98	**Web comments**	NHS Professional 7 (Yorskhire Children's Neuromuscular Service based at Leeds Children's Hospital)	On behalf of the Children's Neuromuscular service, based at the Leeds Children's Hospital and serving the population of North, East and West Yorkshire, we would like to register our concerns in relation to the NICE appraisal for Nusinersen. Whilst Spinal Muscular Atrophy is a rare genetic disorder, we see between 5-10 new cases/year in our region, the majority of whom have the most severe, early onset, type 1 form, associated with rapid, progressive muscle weakness and death in infancy. Therefore, sadly, we have been involved in supporting many families through the unimaginable trauma of watching their babies deteriorate and die. At the same time, we have managed many children with the milder type 2 and 3 forms of the disease as they lose their motor skills and require additional physical and medical care. For example, there are currently 5 children under 5 managed by our service, who did achieve independent standing and walking but who will lose this ability in the next year or so. These are otherwise bright children with normal cognitive functioning who will ultimately become dependent on carers for all their day to day needs with consequent negative effects on quality of life and social participation for the young person and their family. In this context, it has been exciting to witness the development of potential therapies for SMA and in particular to see the clear benefit of a gene modifying therapy (Nusinersen) in 2 international randomised controlled trials (Endear and Cherish). Conducting a robust trial in SMA is hugely challenging given the nature of the diagnosis, and in particular including a placebo arm that required 2 separately blinded teams on each trial site. The methodology and selected end points were clear and relevant in each trial and, appropriately, the trials were stopped at interim analysis when the significant difference in end points between treated and untreated groups were noted. The trials have both been published in highly respected peer reviewed journals and data from these trials and the other open label studies on Nusinersen have been scrutinised by both the EMA and FDA prior to approving a licence for the drug in Europe and the US. As a consequence, the drug is now available and in use across Europe, North America and has been approved for type 1 SMA in Scotland. We note that the NICE appraisal concluded that data was not available for a sufficient period to determine the long-term effectiveness of Nusinersen. Whilst this is true, and an inevitable consequence of the research governance of the trials, there is long term data available from the open label studies, from other international databases in countries where Nusinersen is available and from the Biogen sponsored extended access programme for type 1 SMA in the UK. Data from these sources suggest ongoing benefit from treatment over time, although it is also clear that early treatment confers significant benefits over and above delayed treatment. The UK SMA network has an established natural history database (SMA REACH) which collects standardised data akin to that used for outcome measurements in clinical trials. Thus, there is an existing framework for robust data collection in treated individuals which would serve to answer the question of the long-term benefits of treatment in relation to the natural history. We do not believe that the summaries of the clinical and cost effectiveness reflect the true burden of this disease. The standardised health utilities/modelling tools are designed to evaluate treatment benefits in older individuals and we do not believe they reflect the 'costs' in the SMA population, especially for infants and young children. In particular the models do not include the inevitable costs of progressive weakness in the type 2/3 forms of the disease - spinal surgery, respiratory support, educational and social care packages, or the effect on carers' income and well-being when supporting a severely disabled child. Neither do they capture the costs of supportive treatment in an infant with type 1 SMA which, particularly in relation to critical care bed usage and hospital stays, are considerable. Given the availability of a disease modifying treatment, there is a sea change in expectation and approach to supporting infants with type 1 SMA. This is reflected in the recently updated international consensus statement on standards of care in SMA, a	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA. The company's model, including the approach to reflecting utility and costs, has now changed. This and the committee's view of the changes

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			model of management that we would follow in the UK. A greater number of infants with SMA type 1 are now receiving intensive respiratory support with significant impact on resources both in hospital and in the community. In light of recent high profile legal cases where there was a discrepancy in expectation regarding parents and clinicians views of the infants outcome and potential effects of therapy, it is likely that families, and indeed clinicians, will find it extremely difficult to accept purely palliative/supportive care for infants with SMA as happened in the past. Thus, not choosing to support Nusinersen treatment in SMA is unlikely to be a more cost-efficient solution. We appreciate that the costs of treatment are high but would strongly urge the appraisal committee to review the trial data, in particular the significant benefits conferred by early treatment in infants with type 1 SMA from the Endear and Nurture studies, and in younger children with types 2 and 3 SMA in the Cherish study. We would strongly support a managed access agreement, similar to that between NHSE and PTC therapeutics for Translarna in Duchenne Muscular Dystrophy, to evaluate the role of Nusinersen in the SMA population in the UK. We believe that we have the structures in place in the UK; a strong and effective clinical network and a robust natural history database (SMA REACH), to provide meaningful data regarding the longer term effectiveness of Nusinersen in various SMA populations. Finally, we would ask the committee to consider how a family living in England and Wales should act if their infant is newly diagnosed with SMA type 1 once the Extended Access Programme is closed on 1st November. As you are aware, Biogen have agreed to support ongoing treatment for those already enrolled in the programme but will not support treatment for newly diagnosed cases. Many families will seek treatment in Europe or consider relocating to Scotland. This, of course, is only possible for the more affluent families and thus, in response to the final point regarding discrimination, we believe this decision will discriminate against those families with fewer means, typically in our region this will be the socially deprived South Asian population of West Yorkshire, where we have shown there is a 4.5 x greater chance of developing recessively inherited neuromuscular disorders like SMA. Approved and signed by: [redacted], Consultant Paediatric Neurologist [redacted], Consultant Paediatric Neurologist [redacted], Consultant Paediatric Neurologist [redacted], NM Specialist Care Advisors [redacted], NM Specialist Nurse [redacted], NM Specialist Physiotherapists [redacted],NM Specialist OT	have been captured in sections 3.17, 3.18, and 2.19 of the FAD. Furthermore, section 3.10 of the FAD now addresses early administration of nusinersen.

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			[redacted], Consultant Paediatrician with interest in Neurodisability [redacted] [redacted], Consultant in Paediatric Neurodisability, [redacted] [redacted], Consultant in Paediatric Palliative Care, [redacted] [redacted], Consultant Neurosurgeon, [redacted]	
99	**Web comments**	NHS Professional 8 (Paediatric Neurology Consultant, Neuromuscular team, Sheffield Children's Hospital)	Dear Sir/Madam, I am writing to you on behalf of the Neuromuscular Team in Sheffield Children's Hospital regarding the outcome of the appraisal consultation on nusinersen. Our trust currently sees 14 children with SMA and 7 of them are in the nusinersen EAP program, and one due to start nusinersen therapy on EAP. We would like you to highlight to you our experience of the outcomes for patients with SMA1 receiving nusinersen in terms of their motor/functional abilities/respiratory and perceived quality of life of care givers. In our second part we would like to comment on the way this appraisal has been undertaken. In brief, our 8 patients were of varying ages (8-70 months) and abilities prior to nusinersen. From a motor function wise 3 are now stable sitters. As you know by definition SMA 1 children never achieve sitting. This we think is definitely an improvement in motor function. Furthermore one patient had improved in CHOP score by 23 points in just 18 months post treatment, and is able to kick his legs. There is also significant improvement in head control, upper limb strength and function in 3 of the 8 which leads to ease of feeding, play, ability to partake in social activities and family life better (e.g. going on family holidays as can now tolerate upright posture better). Family and carers find it easier to care for them as they have gained small but significant skills. As our patients have only at most been on nusinersen for 18 months, we believe they may continue to improve in their motor abilities and if not at least not decline. These children are now also able to communicate better. 4 are speaking louder and for longer (in sentences) and 1 is able to communicate better with facial expression and eye-gaze to his carer. One child is now able to put their hand up in class to ask and answer questions and this has resulted in a tremendous improvement in engagement within class and socially with peers. That particular child is also able to sit unsupported on the floor to play at 'circle time' with peers for short periods. The child's confidence has increased. There has been significant decrease in hospital admissions in two patients enabling access to respite care, potentially attend school and participate more in life. The other children did not show an increase in unplanned hospital admissions. Prior to nusinersen some children needed supplementary feeding via PEG because they were so slow at eating. They are now able to eat faster and manage larger quantities such that they now require less or no additional nutritional support.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA. Following

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			At the moment we have not noted any significant improvement in respiratory function but also at the same time have not noted a decline in this, which is the natural history of SMA. We take this as an improvement in what is expected from natural history. We have not noted any significant side effects related to nusinersen therapy. From our cohort it seems patients who are able to access treatment earlier AND are less affected will benefit the most. Thus we feel that 2 of our SMA2 younger children will benefit on nusinersen and so will SMA3 children diagnosed early. We would like to point out how nusinersen was not assessed as a Highly Specialised Therapy when only a few centres in UK are administering it. This is in comparison to cancer drugs which are administered to a larger number of patients but still deemed as a Highly Specialised Therapy by NICE. We feel this is unjust and that nusinersen should be appraised as a Highly Specialised Therapy. We are concerned that NICE has appraised nusinersen and deemed that it did not show long term evidence based on the CHERISH and ENDEAR study. The CHERISH study was terminated early due to significant difference seen earlier than expected. We find that drugs for other conditions e.g. multiple sclerosis also do not show long term evidence but have been approved by NICE. We feel that the data captured and appraised has not given nusinersen justice as certain fields were not considered such as frequency of hospitalisation, child's participation in life and activities, quality of life of care givers, and communication of patient. We appreciate these are difficult to quantify but feel that they are more meaningful to families and affected child. We appreciate that nusinersen may have been costed very highly by Biogen, but having a decision against this drug which has shown definite improvement in many areas for patients with SMA without negotiations would put research and healthcare in the UK at risk of falling behind other developed countries. It discourages investment in healthcare research in the UK, to the detriment of our patients. Sincerely, Dr Min Ong (Consultant Paediatric Neurologist) on behalf of the Neuromuscular Team in Sheffield Children's Hospital, UK.	extensive discussion at scoping, it was agreed that this topic is appropriate for consideration as an STA.
100	**Web comments**	NHS Professional 9 (Evelina Children's Hospital, Guy's & St Thomas' NHS Foundation Trust London, UK)	**Has all the relevant evidence being considered?** In our view the relevant evidence has not been sufficiently considered. In particular, there is no consideration given to the fact that a better response to treatment has been demonstrated when the treatment is given at an early stage of the disease. It is vital to acknowledge that in the clinical trials as well as in the Expanded Access Programme, children receiving treatment very often have wellestablished disease rather than being at a pre-symptomatic or early disease stage. There are sound scientific reasons why earlier treatment would be expected to show better clinical results. In our view it is essential to consider the impact of the treatment not only in children with SMA as a group, but also specifically in those who start treatment at an early stage of the disease.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments

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				including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA. Furthermore, section 3.10 of the FAD now addresses early administration of nusinersen.
101	**Web comments**	NHS Professional 9 (Evelina Children's Hospital, Guy's & St Thomas' NHS Foundation Trust London, UK)	**Concerns regarding the long-term effect of the drug.** Although we understand the committee's concerns regarding potential long-term efficacy of the drug in principle, the published data demonstrate that treated patients show continuing improvement. The long-term effects of the condition SMA are well understood, with early death in infancy in those with type 1 SMA; denying this group of patients an effective treatment on the basis of concerns about either possible long-term efficacy or long-term side-effects seems therefore illogical. Formal postmarketing surveillance is, however, essential to continue to understand the long-term benefits and identify any adverse effects.	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated

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				economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
102	**Web comments**	NHS Professional 9 (Evelina Children's Hospital, Guy's & St Thomas' NHS Foundation Trust London, UK)	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** We do not think that the tools used for this assessment (QUALY measurement) are suitable for the group of patients with a rare, devastating disease such as SMA.	Thank you for your comment. NICE uses cost per QALY for the estimation of cost effectiveness in line with its published methodology, as one of several decision criteria (see sections 5.3 and 6 in NICE's guide to the methods of technology appraisal). This allows a consistent assessment of treatments across the range of diseases and populations appraised by the committee.
103	**Web comments**	NHS Professional 9 (Evelina Children's	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** We do not think that the provisional recommendations are suitable. The recommendations in their current form would deny the group of children with SMA access to the only currently available effective medical treatment. The option then for a child with SMA type 1 would be early death from respiratory failure, or, perhaps more likely nowadays, long-term ventilation pending	Thank you for your comment. The recommendation

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		Hospital, Guy's & St Thomas' NHS Foundation Trust London, UK)	ability to access treatment (during which time there would be deterioration and loss of motor neurons, likely to result in a less good response to subsequent treatment).	s in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
104	**Web comments**	NHS Professional 9 (Evelina Children's Hospital, Guy's & St Thomas' NHS Foundation Trust London, UK)	**Are the boundaries between different subtype of SMA clear or blurred.** The boundaries between different subtypes of SMA, classified on clinical motor milestone grounds which all neuromuscular consultants are familiar with, are very clear. Although there are rare instances of children who fall at the boundaries between 2 subtypes, it is nevertheless possible for experienced neuromuscular consultants to determine the correct subtype. In general, the system used for the classification of SMA is probably one of the simplest classification systems used within clinical medicine.	Thank you for your comment
105	**Web comments**	NHS Professional 9 (Evelina Children's	**Requested comments on whether there is a clinically distinct subgroup of people in whom nusinersen is expected to have better efficacy.** There is a subgroup predicted not to respond: those with no copies of the SMN 2 gene (routinely established on genetic testing of any child with SMA). Those children at more advanced stages of the disease process would be expected to show	Thank you for your comment. The responses to NICE's specific

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		Hospital, Guy's & St Thomas' NHS Foundation Trust London, UK)	less benefit.	questions on clinically distinct subgroups fed into a workshop conducted by NICE to discuss these issues with clinical and patient experts.
106	**Web comments**	Member of the public	Spinraza has been shown to have significant benefit in those countries that have adopted and funded it and as usual the UK is lagging behind with a negative, indecisive outlook. It is at present the only treatment available (subject to funding) and does benefit recipients. Fund it!	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
107	**Web comments**	Member of the public	A complete travesty of a decision for anyone suffering from SMA and their friends and family. If this outcome is financially driven, then I'm even more disgusted given the fact that this treatment has proven results for a condition that currently has no alternative. Please consider that time is crucial for those with SMA and find a way of resolving this quickly, with compassion for	Thank you for your comment. The

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			those that this decision affects.	recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients, carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.
108	**Web comments**	Member of the public	Why oh why is the UK dragging its heels yet again. How many children/families will have to suffer whilst the powers that be procrastinate. This treatment will enable all involved to have better lives. What will be the cost of the 24 hour care in all aspects of everyday life that is waiting for children with this terrible condition?	Thank you for your comment. The recommendations in the Final Appraisal Document (FAD) have changed. The committee have taken into account the consultation comments including the views of patients,

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				carers and clinical experts alongside the updated economic model and proposed MAA. Nusinersen is now recommended for pre-symptomatic and types 1, 2, and 3 SMA in the context of a MAA.

Single technology appraisal

Nusinersen for treating spinal muscular atrophy [ID1069]

Dear Consultees and Commentators

We are actively engaging with Biogen to discuss how they might address the uncertainties identified by the committee, while demonstrating the potential for nusinersen to be considered cost effective and managing the risk to the NHS of allowing access to this treatment.

During the appraisal process the committee heard that nusinersen may have a relatively greater benefit for those with more severe types of SMA, but that the classification system does not always reflect the full extent of the disease. Boundaries between the different SMA classifications are blurred and can be subjective.

As part of your response to consultation we would welcome your comments on whether there is a clinically distinct subgroup of people in whom nusinersen is expected to be more clinically effective, and how this group could be identified in clinical practice.

Yours sincerely,

Helen Knight

Programme Director, Centre for Health Technology Evaluation

Nusinersen for treating spinal muscular atrophy

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5:00pm on 05/09/18

	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):	Biogen Idec Ltd.
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:	Michael Tempest

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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Nusinersen for treating spinal muscular atrophy

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5:00pm on 05/09/18

1	Biogen appreciate the opportunity to provide comments on the NICE Appraisal Consultation Document (ACD) for nusinersen for treating spinal muscular atrophy (SMA) [ID1069]. Biogen are disappointed that the Appraisal Committee was unable to recommend nusinersen in the ACD, however, we are committed to collaboratively finding solutions that address the remaining uncertainties, mitigate risk to the NHS and ensure that access to nusinersen is managed appropriately without further undue delay. In addition, Biogen believe that several conclusions in the ACD are not an accurate interpretation of the evidence and encourage the Appraisal Committee to reconsider its conclusions, as described in the following comments. To support the comments, Biogen have submitted an appendix containing clinical data that explain the long-term model assumptions. The clinical data also clarify the health benefits beyond the primary trial endpoints of survival and motor function. Furthermore, Biogen have put forward a revised commercial offer for consideration. The revisions reduce the ICERs within ranges that may be deemed cost-effective pending further data collection. In parallel, Biogen are continuing to develop a proposal for a managed access agreement (MAA) for consideration by the committee in October.
2	Paragraph 1.2 notes that there is an unmet need for effective treatments that could slow disease progression. We are concerned that this recommendation may imply that the unmet need is similar across infantile onset (type I) and later onset (types II and III) SMA. Patients with infantile onset SMA fail to develop any motor milestones and rarely survive to their second birthday without permanent ventilation.(1,2) Standard of care only helps to prolong survival of infantile onset patients through highly invasive tracheotomy or permanent ventilation, and it does not slow or prevent the decline of motor and respiratory function.(3) Therefore, given the rapid functional decline in patients with infantile onset SMA, there is an urgent unmet need for an effective treatment that significantly extends life without permanent ventilation, and allows a child to develop any motor functions that are not possible with the current standard of care. In contrast, patients with later onset SMA are expected to survive until adults, albeit with a progressive loss of motor function and independence.(4–7) Standard of care is aimed at relieving the symptoms, but it does not slow or prevent the decline of motor and respiratory function.(3) For these patients, the progressive decline and loss of ability can have significant impacts on fundamental daily life activities including self-feeding, turning in bed alone, using the restrooms alone, washing by themselves and perform transfers.(8) Therefore, the major unmet need for patients with later onset SMA is to stabilise or improve the current physical condition of patients in relation to muscle strength, respiratory function and mobility/functionality, improving health-related quality of life (HRQoL) and reducing the dependence on carers.(6,8) It is important that the unmet needs and potential benefits with effective, disease-modifying treatment are defined respectively for the 2 patient populations given the different challenges faced by patients, families and their carers.
3	Paragraph 3.1 illustrates SMA as a spectrum disorder but we are concerned about the way in which the level of motor milestones achieved and survival outcomes for type I and II SMA have been depicted. Type I SMA has been described as severe muscle weakness which affects movement, swallowing

	and breathing. However, for a true description of the disease severity, the wording should be revised to note the 2 year life expectancy of patients and the failure of patients to develop any new motor milestones after maximal motor milestones are achieved (as described by Farrar et al, 2017).(1) Likewise, patients with type II SMA have been described as being 'severely disabled' and 'unable to walk unaided', which is a generalisation that does not fully reflect the condition. In reality, although these patients survive to adulthood, they still have a shortened life expectancy compared to the general population.(1,9,10) The maximal motor milestone achieved is walking with assistance, although some type II patients only ever achieve sitting unaided before declining.(11) Patients are also at a high risk of developing scoliosis.(11) Therefore, the description should be revised accordingly. Furthermore, it should be noted that patients have normal intelligence and are fully aware of their fate and the limitations of current standard of care.(12). The associated fear of losing abilities and independence imposes a major psychological burden on patients and carers as consistently cited in numerous statements from the patient advisory group submissions.(8,13,14)
4	Paragraph 3.1 mentions that SMA classification is blurred and can be subjective. Although it should be acknowledged that SMA is a spectrum disorder it is still possible to classify patients by maximal motor milestone achieved. Patients may reach milestones at the margins of subtypes, and may be referred to as a severe type II or a mild type I, but are still recognised according to the main subtype.(9) Furthermore, 80% of patients with SMA type I carry 1-2 copies of the SMN2 gene, 82% of patients with SMA type II carry 3 SMN2 copies, and 96% of patients with type III SMA carry 3-4 SMN2 copies.(15) Therefore, SMN2 copy number is also used as a key determinant of disease phenotype and is routinely determined after initial diagnosis to help predict the clinical phenotype.
5	Paragraph 3.2 notes the impacts of SMA on HRQoL, particularly for carers. However, the methodology for assessing caregivers' quality of life is not well developed and there is little evidence about the impact of SMA on caregivers' HRQoL or other important facets of their lives. For example, the sleep deprivation associated with infants needing to be turned a number of times during the night,(8) can be difficult to capture with available instruments. Furthermore, more than one caregiver may be affected, and this may extend beyond the immediate family. A patient survey conducted in Scotland(6) reported that, out of 19 children and adults with SMA, unpaid care was provided by parents (n=16), grandparents or other relatives (n=11), friends (n=4), a partner (n=1), a son/daughter (n=1) or someone else (relationship not disclosed; n=1). A large proportion of the carers had given up work completely (n=42%) or dropped to part-time (37%) due to their caring responsibilities. As is noted as part of the HTA assessment in Ataluren for Duchenne Muscular Atrophy(16), the ERG accounted for 2 caregivers as part of the economic model. From the patient perspective, the range of impacts on patients' HRQoL of diminished educational opportunities or reduced integration into society are also difficult to capture using available HRQoL measures. In children and young people, general issues surrounding the assessment of HRQoL have been addressed in a number of studies. A systematic review by Vaidya (2018)(17) found that, while the PedsQL instrument used as the basis for calculating quality-adjusted life years (QALYs) in the company submission was the most commonly used tool in SMA, no disease-specific tool had been developed for SMA and there is no measurement tool for very young infants (less than 12 months) with SMA type I. Vaidya and Thompson (2017)(18) suggest that a range of instruments, including disease-specific measures, is likely to be required to inform decision-making. Among SMA types II and III, SMA-Europe member organisations (Rouault et al. [2017)(8)] conducted a survey across Europe to explore the importance from the patient's perspective of daily functions and physical

	condition for their HRQoL. They concluded that tools were still needed that measure functionality and that can be translated into daily life actions of importance to patients.
6	Paragraph 3.3 mentions the unmet need for SMA patients and lack of disease-modifying treatments, however Biogen are concerned that the extent of the unmet need is not clear enough. As highlighted by the patient and clinical experts, current treatments do not affect disease progression. Without access to a disease-modifying treatment, patients not only face the loss of motor function, but also premature death which is expected to be, on average, 2 years after diagnosis in patients with type I SMA.(1) Furthermore, as patients with SMA have normal intelligence,(12) they are aware of their fate, and this (along with the symptoms experienced) has a significant impact on HRQoL. The urgency to treat should also be noted. The lack of access to a disease-modifying treatment is a time-critical issue due to the progressive neuronal loss and reduced length of life facing patients.(19) The benefits of earlier treatment of nusinersen have been highlighted through subgroup analyses conducted for the later onset population of CHERISH and the infantile onset population of ENDEAR. In the infantile onset population, earlier and greater motor milestone responses and prolonged survival were observed among patients with shorter disease duration at the start of the study (≤12 weeks) compared to patients with a longer disease duration (>12 weeks), suggesting that on average early treatment with nusinersen may confer a stronger benefit. In CHERISH, nusinersen-treated children who were younger and had shorter disease durations generally showed the greatest improvements in HFMSE from baseline; older children and those with longer disease durations demonstrated stabilisation of HFMSE scores in comparison to a decline seen in the sham arm; this is consistent with the idea that early initiation of treatment may lead to greater improvements. Therefore, it is preferred that the wording is revised to stress the extreme and time-critical extent of unmet need to help put the value offered by nusinersen, a disease-modifying treatment, into context.
7	Paragraph 3.1 and 3.4 stress the lack of evidence in type 0 and IV as well as the potential issues in genetic testing and delays in treatment. The ACD states that “However, the clinical experts stated that gene testing may lead to delays in starting treatment.” Biogen are not aware of evidence that gene testing may lead to delays in starting treatment. Diagnostic delays are indeed common in SMA, which may have a negative impact on families; SMA symptoms can vary widely in onset and severity and can resemble other diseases and a lack of awareness or expertise of SMA means that healthcare professionals may often consider other diagnoses before SMA.(20,21) In this respect there have been calls for a new-born screening programme to help speed up the diagnosis of SMA. Biogen are committed to helping improve the early diagnosis of SMA. The ACD also states that “Moreover, they considered the correlation between copy number and disease severity is much less reliable than the clinical classification system in identifying the likely course of SMA”; however as described in comment number 4, *SMN2* copy number is also used as a key determinant of disease phenotype in conjunction with the clinical classification system, with neither system being completely robust for what is a spectrum disease. The ACD states that “The committee acknowledged that nusinersen should be considered within its marketing authorisation (that is, for all types of SMA) but the company had not presented evidence for

	type 0 and type 4 SMA." Biogen are pleased that the committee have acknowledged that nusinersen should be considered within its marketing authorisation i.e. for all types of SMA. The company's restricted submission is aligned with available clinical data i.e. in infantile onset SMA (type I) and later onset SMA (type II and III) and ability to conduct an economic analysis. However, it should be noted that types I-III capture the majority of SMA cases; SMA type I, II and III are reported to constitute 60%, 27% and 12% of all SMA cases,(22) respectively; data on type 0 and IV are limited because they are rarely diagnosed. Clinicians have questioned whether type 0 treatment may be futile. Based on the underlying disease pathophysiology and the mechanism of action of nusinersen(23), there is good reason to believe that nusinersen could benefit patients with type IV SMA, however without evidence it is not possible to quantify the size or duration of benefit. Biogen are continuously assessing data generation efforts for the population with type IV SMA.
8	Paragraph 3.5 notes that the evidence was suitable for decision making despite its uncertainties. Biogen note that the limitations identified in the ENDEAR and CHERISH trials should be viewed in the context of the difficulties of conducting trials in orphan diseases, with the clinical trial development programme for nusinersen being one of the largest for an orphan indication. Specific limitations with the trial data addressed here are: • a different dosing schedule in the CHERISH trial compared with the marketing authorisation • the (more homogeneous) patient composition of the CHERISH trial compared with clinical practice • the short follow-up periods in the ENDEAR and CHERISH trials In relation to the dosing schedule, the clinical development plan evaluated a range of single and multiple doses of 1 mg to 12 mg of nusinersen. Several different loading dose regimens and 2 different maintenance dose regimens have also been evaluated. This allowed the dosing regimen to be refined over time based upon emerging results from the clinical trials. The licensed dosing is with 4 loading doses on days 0, 14, 28 and 63, with a maintenance dose administered once every 4 months thereafter. In CHERISH, nusinersen was administered using 3 loading doses (on study days 1, 29 and 85), followed by maintenance dosing 6 months thereafter (on day 274). The recommended licensed dose of 12 mg was used in CHERISH. The impact of this and the more homogeneous patient composition of the CHERISH trial compared with clinical practice on the trial results is unknown although they will not necessarily be in nusinersen's favour. It is anticipated that the more intensive loading dose interval used in the licensed dosing vs that used in CHERISH (i.e. 4 vs 3 loading doses and maintenance dose at every 4 months vs 6 months) would not lessen the efficacy of nusinersen in later onset SMA patients (if anything, it may improve efficacy). The short follow-up periods in the ENDEAR and CHERISH trials are due to the extremely positive results at interim analysis points and the view of independent ethical review committees that it would be unethical to proceed with the trials. While the limitations of the ENDEAR and CHERISH trials are acknowledged in terms of duration of follow-up, subjects in both trials were given the opportunity to join the SHINE study and other studies to additionally provide longer term and real-world evidence to inform decision making. Interim results (30th June 2017) of the SHINE study showed that patients receiving nusinersen in both

	ENDEAR and SHINE studies had significantly better outcomes than those who were in the sham procedure control group in ENDEAR and in the nusinersen group in SHINE on key endpoints of overall survival and median time to death or permanent ventilation (see Appendix 1). Those continuing with nusinersen in SHINE experienced new improvements in motor milestones (Hammersmith Infant Neurological Examination [HINE-2]) and general motor function (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders [CHOP INTEND]). The analysis showed that improvements in motor milestones are achieved whatever the age of treatment initiation, but benefits are generally greater with early treatment. These findings are also supported by longer-term data from the phase II study CS3A in type I patients, in which patients have been assessed over a 3.5-year treatment period), and the phase I study CS2 and its extension CS12 in type II and III patients (treated for 2.2 years). These studies support the maintenance of effect with long-term treatment beyond the age of 24 months and show the robust nature of the clinical trial programme in this orphan rare disease area.(23)
9	Paragraph 3.6 mentions that the ENDEAR trial was stopped early due to the strength of the survival benefit, however Biogen would like to request amendment of the reason for stopping the trial. Overall, the ENDEAR trial was stopped early due to the efficacy observed in the nusinersen group compared to the sham control group and ethical consideration for the infants in the control group.(24) The first primary endpoint was a motor-milestone response (defined according to results on the HINE-2) and the second primary endpoint was event-free survival (time to death or the use of permanent assisted ventilation).(24) Only the first primary endpoint was analysed at the interim analysis, while all the other endpoints were analysed at the final analysis. In the interim analysis, a significantly higher percentage of infants in the nusinersen group than in the control group had a motor-milestone response (21 of 51 infants [41%] vs. 0 of 27 [0%], P<0.001), and this result prompted early termination of the trial.(24) In the final analysis, a significantly higher percentage of infants in the nusinersen group than in the control group had a motor-milestone response (37 of 73 infants [51%] vs. 0 of 37 [0%]), and the likelihood of event-free survival was higher in the nusinersen group than in the control group (hazard ratio for death or the use of permanent assisted ventilation, 0.53; P = 0.005). Overall, the interim results for improvement in motor milestones were so compelling compared to sham procedure that the study was concluded and infants were moved to the open-label extension study SHINE.
10	Paragraph 3.7 notes that outcomes reported in ENDEAR, such as respiratory function, time on ventilator and hospitalisations cannot be reported because they are academic in confidence (AIC). It is stated that the committee considered these outcomes did not show a substantial benefit and found it counterintuitive that a substantial survival outcome was not associated with a substantial benefit in other outcomes. Due to the small patient population in SMA it is difficult to power multiple trials to test multiple endpoints and hypotheses. ENDEAR and CHERISH were powered and designed to show survival and motor improvement, which they have demonstrated. The trials were not designed to specifically look at respiration; they were not powered to detect differences between the groups in respiratory outcomes, which would need a much larger cohort. As we heard in the AC meeting from the NICE elected clinical advisor, it is very difficult to measure respiratory function in infants. Hours on ventilation is the most appropriate scale for infants with SMA, however it is very subjective. In addition, respiratory outcomes would be confounded by the time of year that the therapy was initiated. If rescue of respiratory function had not yet occurred during the winter months in the ENDEAR trial then additional lung tissue damage could have occurred from recurrent severe viral infections. Lung function would also be hampered by frequency and number of aspirations, which is also partially dependent on the gastrointestinal approach adopted for each

	patient. Despite all the above barriers and confounders listed above statistical benefit on ventilation is still shown with nusinersen therapy (see Appendix 1 Section 1.3). Without prejudging what the committee considers to be a substantial benefit, the trial results show that, in addition to survival benefits, nusinersen also had a beneficial impact in terms of ventilation and hospitalisation. These show that a significantly higher proportion of nusinersen treated patients compared with sham procedure control patients survived without permanent ventilation at the end of the study and, among infants not requiring ventilation support at baseline, a significantly higher proportion in the nusinersen group did not require initiation of ventilation support while on the study (Parsons et al., 2018) (see Appendix 1; section 1.2). Overall time spent hospitalised and time spent hospitalised for respiratory reasons were both significantly lower in the nusinersen group compared with the sham procedure control group (Tulinius et al., 2018) (see Appendix 1; section 1.3). Please note that the AIC label can now be removed from the ENDEAR trial results as they have been the subject of the above conference presentations.
11	Paragraph 3.8 noted that nusinersen significantly improved motor function of children with later onset SMA but it was unclear how this affects survival because there were no deaths during the CHERISH trial. The relationship between motor function and survival is particularly relevant to later onset (type II and III) patients as life expectancy is not reported to be significantly less than that in a normal population. Pulmonary disease, secondary to inspiratory and expiratory muscle weakness, is the primary cause of both morbidity and mortality in patients with type II SMA (Wang et al., 2007). Kaufmann et al. (2012) found that pulmonary and motor function outcomes both declined in patients with types II and III SMA over observation periods exceeding 1 year. However, while nusinersen is associated with an impact in the long term on both motor function and survival, this relationship cannot be quantified from the clinical trials. It should be emphasised that type II SMA encompasses a wide spectrum of patients, with a correspondingly wide range of levels of motor function and of mortality.
12	Paragraph 3.9 highlights the uncertainties associated with nusinersen. Although Biogen agree that there are uncertainties in the absence of data, we are concerned that this uncertainty has been overstated. The nusinersen clinical development programme is the largest body of evidence for an interventional approach in SMA, with over 5 years of data. The mechanism of action of nusinersen combined with the observed data to date, indicates that the effects of nusinersen can be sustained in the long-term. Overall, nusinersen has demonstrated favourable efficacy and tolerability in clinical trials and clinical practice for patients with SMA, with no evidence of a lessening of effect over time. Biogen are committed to collecting long-term data and addressing the surrounding uncertainties. Data from SHINE have recently become available (of which the latest evidence is presented in Appendix 1, section 1.1 (see separate document)), showing the longer-term benefits of nusinersen including improvements in motor function and increased event-free survival in patients followed for nearly 3 years. Following suggestions form the EMA, Biogen is supporting prospective, non-interventional studies (registries) of patients receiving and not receiving nusinersen to provide further evidence of efficacy and safety of the therapy. Biogen are also continuing to develop a proposal for a MAA for consideration by the committee in October.

Nusinersen for treating spinal muscular atrophy

NICE National Institute for Health and Care Excellence

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13	Paragraph 3.10 noted that the model structure was based solely on motor milestones and that the structure was consistent with the main outcomes of the clinical trials. At the same time, the evidence review group (ERG) explained that motor function was not the only factor affecting HRQoL. The committee concluded that the models had limitations but were suitable for decision making. We concur with the committee that the economic model structures were chosen to be aligned with the main clinical trial outcomes. We also agree with the ERG that motor function is not the only factor affecting HRQoL and argue that a broad perspective on patient outcomes should be taken. HRQoL data collected in the CHERISH trial using a broad-based instrument (the Paediatric Quality of Life Inventory (PedsQL)) were used as the basis for estimating QALYs in infantile and later onset SMA as no HRQoL measures are available for infants. Caregivers completed the questionnaires as proxies where patients were unable to. However, the assessment of HRQoL is extremely difficult in children and young people with SMA for a number of reasons. First, young children undergo dramatic changes in growth and function at different rates, so it is difficult to evaluate the effect of a health intervention.(25) Second, current generic measures, except Health Utility Index Mark 2, are derived from adult populations, so additional attributes relevant to children, for example autonomy, body image, and family relationships, may not be captured by these measures.(25) Conceptually, HRQoL for children, particularly infants, will depend on different factors from those important to adults. Therefore, when used as proxies, caregivers may not represent patients adequately and instead capture their own anxieties due to the illness.(25,26) Currently, there is no generic instrument for measuring HRQoL in infants and children younger than 5, highlighting the challenge of deriving utility values in this population. Young children usually do not have the cognitive ability to understand and complete valuation or even measurement tasks.(25). Although the PedsQL measure is frequently used in SMA, and there is some evidence for its validity, reservations have been expressed about this instrument. Where treatment is expected to improve survival (particularly in early onset) beyond the normal life expectancy of patients with SMA, there is no experience on which to base HRQoL assessments. Therefore, at this moment in time, clinical judgement is the best approach to address the uncertainties in HRQoL. Furthermore, as also described in comments 19 and 20, QALYs are unlikely to capture all the important aspects of HRQoL in these patients. Reducing a patient's life experience to a single number on the EQ-5D scale is unlikely to be sufficiently sensitive to capture all aspects of HRQoL for SMA. For example, ability to communicate and grasp objects will not be detected using generic measures, but these represent important improvements in a child's development. In the absence of directly assessed utilities (e.g. EQ-5D questionnaire), a mapping algorithm was used to convert PedsQL data into EQ-5D but it may not be generalisable specifically to SMA patients. Furthermore, utilities for any given health state are assumed to be constant over time, which is unlikely to reflect real life. Comment 5 describes other factors impacting the HRQoL of patients with SMA, that are not possible to represent through the methods preferred by NICE to estimate QALYs.
14	Paragraph 3.11 noted that the assumption underlying the transition probabilities used in the models that those treated with best supportive care could not get better was, according to the ERG, inconsistent with the observed trial data, in which a small proportion of people receiving sham therapy had improvements in symptoms over almost all time periods. On the other hand, clinical experts thought it possible that early onset SMA would progressively worsen if left untreated but that some patients taking nusinersen could worsen.

	Worsening of some patients treated with nusinersen in clinical practice may reflect the difference between trial populations and the prevalent population with SMA as well as the urgency to treat early to maximise the chances of success. Heterogeneity of response between patients treated with nusinersen is acknowledged. However, the model structure is not designed to have a one to one correspondence between trial patients and the modelled cohort. Beyond the end of trial follow-up, the most appropriate approach was considered to be to use the mean changes for trial patients as a whole. This was supported by a clinical advisory group, and continuing improvements beyond the end of trial follow-up in ENDEAR have been reported in the SHINE study. Recently published data from SHINE (presented in Appendix 1 (see separate document)) show improvements in motor function and increased event-free survival in patients followed for nearly 3 years. For patients receiving best supportive care, a number of studies have shown that the natural history of SMA is characterised by a worsening of the condition. Kaufmann et al. (2012) found that motor and pulmonary function declined over time in patients with types II and III SMA, particularly at time points beyond 12 months of follow-up. Mercuri et al. (2016) found a mean decline in Hammersmith Functional Motor Scale Expanded (HFMSE) scores over a 12 month period in patients with types II or III SMA. Type III SMA can be further divided into subtypes IIIa and IIIb. Children with type IIIa and IIIb develop symptoms between 18 months and 12 years and are frequently able to walk at the point of diagnosis. However, although patients with SMA type IIIb have a 97% probability of walking 10 years after diagnosis, the probability reduces to 73% for children with SMA type IIIa.(1) Over a follow-up period of up to 40 years, Zerres et al. (1997) show a decline in the probability of being able to walk in patients with types IIIa and IIIb SMA.
15	Paragraph 3.12 notes that, in better health states, the models apply a similar mortality risk to patients with less severe types of SMA, with the ERG observing that the overall survival benefit of nusinersen was driven mainly by this mortality adjustment and considering it optimistic, as did the committee. While the long-term impact of nusinersen on survival is uncertain, and the assumptions used to model may be considered optimistic, as they were by one of the clinical advisers, the ERG reports that the other clinical adviser thought the survival curves reasonable. Clinical experts support the proposition that the preservation of respiratory muscle function should translate into a long term survival benefit but, in the absence of long term data, quantifying the magnitude of this benefit is challenging. Indeed, the ERG's own preferred analysis adopted the same approach to survival, suggesting that, while this analysis did not address concerns around the plausibility of the company's survival extrapolation, it is a not unreasonable 'base case'. Ultimately, longer term data is needed to assess whether this approach gives realistic survival estimates.
16	Paragraph 3.13 notes that the ERG considered the patient utilities used in the company's models to lack face validity, preferring a vignette study based on European Quality of Life-5 Dimensions (EQ-5D) assessments by healthcare professionals to the mapping of PedsQL data to EQ-5D. The committee considered that both approaches had serious limitations but that it would take account of both in its decision making. As acknowledged by Biogen, the point raised by the committee illustrates the inherent challenges associated with capturing HRQoL and utility data in SMA, especially for infants and young children and highlights questions around the appropriateness of using a single metric such as the QALY to

	assess the value of nusinersen. In the absence of HRQoL or utilities available from the ENDEAR trial, the vignette study was undertaken to generate utilities for early onset patients. At the same time, given the limitations (as described in comment 13) of the algorithm mapping PedsQL to EQ-5D for the later onset population, the vignette approach has some advantages if the initial small sample of clinicians in which the study was undertaken can be increased. The impact on the cost-effectiveness results in later onset SMA of using the ERG's approach rather than the company's approach demonstrates the importance to the results of the way in which HRQoL and utilities are assessed. In the absence of a well validated SMA-specific HRQoL instrument, consideration needs to be given to the best way of capturing HRQoL within any MAA.
17	Paragraph 3.14 noted that the ERG had critically appraised the assumptions behind the company's approach to carer utilities but that its proposed alternative was considered by the committee to lack face validity. Biogen agree with the committee that the ERG approach lacks face validity. In infantile onset SMA, the health state with the highest patient utility had lower carer utility than all other states apart from 1 of the 2 states with the joint lowest patient utility (the 2 states had patient utility of -0.24 and carer utilities of 0 and 0.85, respectively). In later onset SMA, the 2 states with the joint highest patient utility had lower carer utility than all other states apart from the 2 with the joint lowest carer utility (both with utility of 0). It is counterintuitive that inclusion of carer QALYs should increase the incremental cost-effectiveness ratios (ICERs) as in the ERG analysis. Currently, the methodology for incorporating carer QALYs into the analysis is underdeveloped and neither the company approach nor the ERG approach provides a satisfactory solution. An alternative method needs to be developed and consideration given to the number of caregivers affected (as was done in the NICE appraisal of ataluren) given the demands placed on families and caregivers by the degree of dependency seen in SMA. Biogen have provided exploratory analyses for caregiver QoL in a separate appendix. Biogen would like to re-iterate the substantial burden on family carers, impacting on their HRQL and posing a substantial economic burden on SMA families, and wider society. A high proportion of working parents with SMA have to reduce or even leave their jobs, leading to financial strain and further impacting on their HRQL(27) A survey of SMA families in Scotland (n=19; n=2 with type I or II, n=17 with type II or III) found that 79% (n=15/19) of the main unpaid carers had to give up work completely or drop to part time.(6) Parents of children with SMA (total of 12 replies across types I-III) reported that they attend 2–6 appointments per month in connection with their child's SMA, and 6 (50%) estimated they spend over 20 hours per month in connection with these appointments.(6) As the disease progresses, patients require more intensive treatments. The impact on carer's lives was also captured in the survey based on representative comments from family carers regarding the challenges of looking after a child with SMA, as follows(6): • Parent of young person age 16 with SMA type II: The biggest challenge in having a child with SMA is learning to adapt your life to meet the needs of your child not just the physical and emotional demands but the financial demands as well as anything needed for a child with a disability comes with a huge price tag. • Parent of child age 2 with SMA type II: Turning 4 times a night and monitoring the ventilation up to ten times a night. We always have to take care of the needs of our baby by ourselves and spend countless hours trying to give them the care (physiotherapy) they should be receiving from professionals by ourselves.

	• Parent of a young person age 11 with SMA type III: Tiredness, backache, lack of time for myself, lack of time for other child, stress. • Parent of a child age 19 – 35 months with SMA type I / II (specific age not given): At such a young age the biggest concern for us is our mental preparation for physical deterioration and the problems we will face as a family. • Parent of a child age 9 with SMA type III: Taking time out of work to attend appointments. Constantly 'pushing' to get what our child needs / not feeling that we are doing enough. Emotional difficulties/distress and extra stress. Extra vigilance, worry and uncertainty about everyday activities and about what the future holds for our child. Challenging to help child be as independent as possible, and to fulfil their potential. Sibling relationship management.
18	Paragraph 3.15 noted the committee's conclusion, taking into account the company's cost-effectiveness estimates and the ERG's estimates (including the exploratory analyses increasing the ICER by up to £200,000 per QALY), that the ICER based on the list price could reasonably be predicted at between £400,000 and £600,000 per QALY but may be higher. A number of factors contribute to a large element of uncertainty in the estimates of cost-effectiveness. These relate to the challenges of demonstrating long term benefits given the early termination, after positive interim findings of the pivotal trials and considering the sparse nature of additional data to aid the extrapolation of survival and their lack of alignment with standards of care in the UK. Other uncertainties relate to the conceptual and practical issues surrounding the assessment of HRQoL and utilities in this patient group and quantifying the impact on carers.
19	Paragraph 3.17 explains that nusinersen has been recognised as innovative but that these benefits have not been captured. Biogen are pleased that the appraisal committee have recognised the innovation of nusinersen, however they are concerned that the committee feel that the economic analyses have not captured any data to show distinct and substantial benefits relating to the innovative nature of nusinersen. Current standard of care cannot result in improved survival, stabilisation and improvement of motor milestones as shown with nusinersen, which is a clear indication of the innovative nature of the drug. The clinically meaningful improvements in motor function (for example being able to improve or maintain the ability to self-feed, have a wash independently, use the bathroom independently and perform transfers alone to name but a few), together with significant improvements in event-free survival will help to alleviate the profound physical and psychosocial burden experienced by patients and carers.(13,14,28,29) Biogen believe that due to the conservative-nature of the economic model, it does not fully capture the clinical, psychological and social impact that an efficacious disease-modifying treatment will have on patients with SMA and their carers. As described by McGraw et al "*just the difference between not being able to move a finger and being able to move a finger by half an inch can mean the difference between being able to operate a motorized wheelchair or not, and that makes a huge impact on their quality of life and on their ability to be independent*".(14) Improvements such as this do not occur in untreated patients as part of the natural history of disease. Furthermore, stabilisation of the disease is also considered to a be clinically significant advance in patients(8) in this progressive disease, and this is also not fully captured in the economic model. As another example, it has recently been reported that ambulatory children treated with nusinersen in the CS2/CS12 study demonstrated improvements in ambulatory function, as determined by the 6-minute walking test (6MWT), with increases in walking distance and stabilisation or decreases in

	fatigue.(30) While there is no precedent for improvements like these in SMA, changes of ≥30 meters are considered clinically meaningful and thought to impact everyday activities in other paediatric neuromuscular disorders.(31) Decreasing fatigue with corresponding increases in distance walked during the 6MWT may represent a treatment effect. Nusinersen is the only treatment that can change the course of the disease in this manner, and not all of these factors such as improving fatigue have been captured in the economic model. In addition, there are several clinical aspects that were not captured in the nusinersen clinical trials and therefore not the models; it is likely that the innovative benefits of nusinersen will help to mitigate at least some of these. In this way it is likely that the base case for the economic model represents a conservative estimation. These areas include: 1. Swallow, time it takes to feed child and make up feeds 2. Speech and other forms of communication 3. Weight over/under gain 4. Aspiration frequency 5. Cough and time required for chest physio and cough assist 6. Pain 7. Contracture management / contracture stretching 8. Fracture frequency and management 9. Joint dislocation 10. Gut dysmotility and constipation 11. Pressure sores and their management 12. Phycological impact 13. Impact on siblings and family 14. Frequency of infections 15. Scoliosis 16. Broader lung function tests in older children The clinical trial programme includes pre-symptomatic patients that in a real word setting would be identified by new-born screening (NURTURE). The data show that the greatest improvements in total HINE-2 motor milestones were observed in infants treated with nusinersen in the pre-symptomatic stage of SMA in NURTURE as illustrated in the figure below. However, these results were not included in the economic model, which again shows the conservative nature of the model. **HINE-2 motor milestone scores across studies**

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	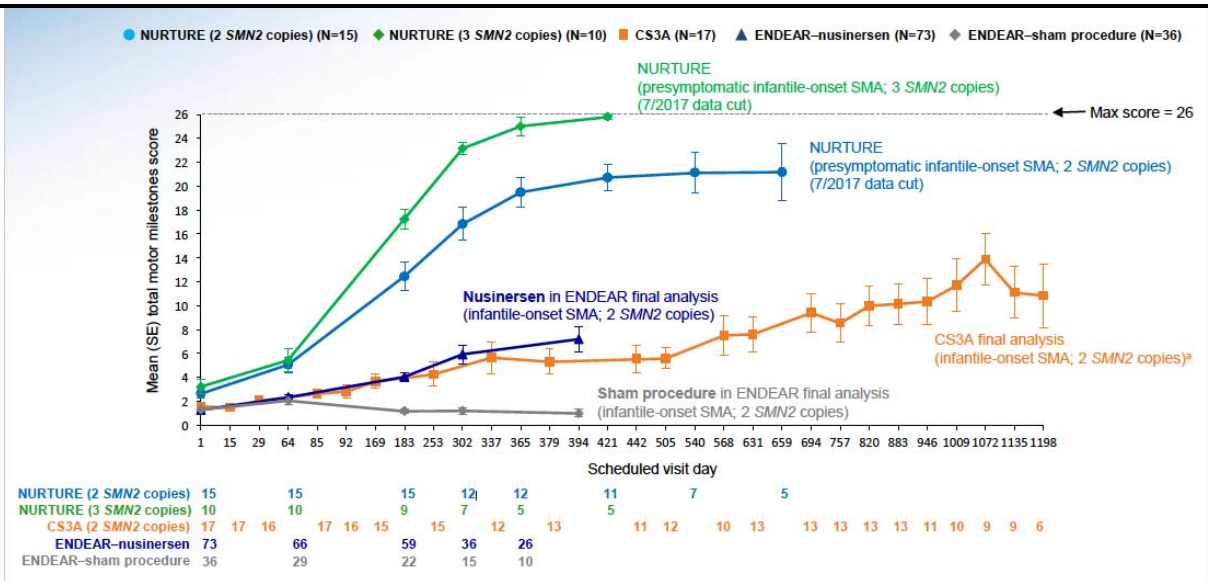 Abbreviations: HINE-2, Module 2 of the Hammersmith Infant Neurological Examination; SE, standard error, SMA, spinal muscular atrophy; SMN, survival motor neuron NURTURE study interim analysis data cut-off date: July 5, 2017. aCS3a end of study data for the cohort of infants with 2 *SMN2* copies. Please note all patients in the figure have 2 copies of *SMN2* except the green nurture line. This is for clarity of comparison Source: Finkel 2018(32) Finally, it should be noted that the availability of nusinersen in England and Wales will help foster investments in drug innovation for patients in other currently underserved rare disease areas. In particular, the development of nusinersen has involved many decades of research into optimising antisense technology - this technology now has the potential to have a significant effect on the treatment of other neurological conditions in the near future.(33) In addition, the clinical trial design (a randomised controlled trial with a sham control), in a large number of patients for a rare disease, with validated and clinically meaningful outcomes, also represents an innovation which may be emulated for other rare diseases. Overall, the innovative nature of nusinersen for the treatment of this devasting rare disease aligns with the Department of Health's UK Strategy for Rare Diseases to provide patient access to beneficial innovations.(34)
20	Paragraph 3.18 noted the committee's consideration of whether there were any health benefits not captured in the analysis and its conclusion that it was difficult to assess how they might affect the cost-effectiveness estimates. One of the difficulties with capturing the health benefits of nusinersen, aside from those associated with evaluating QoL in infants and children, is determining the most appropriate QoL tool for children with SMA. A recent systematic literature review found that the Paediatric Quality of Life Inventory was the most commonly used tool to measure QoL in children, but there were no disease-specific tools to capture QoL in children with SMA.(17) Therefore, it is highly likely that QoL benefits attributable to nusinersen weren't fully captured with generic tools, specifically given the multiple contexts affected and limited by their disease in relation to peer group, family, classroom and community.(17) Secondly, health benefits were captured from a range of ages in the CHERISH trial using the same instrument;

	however, the cognitive differences vary substantially between each year in a child's development.(17) Therefore, it is likely that the same QoL tool will capture different health benefits for children aged 2-4 years old than for children aged 8-12 years old. Furthermore, as recognised by Vaidya et al (2018), SMA presents at different ages and subsequently in different types/severity levels which makes it particularly challenging to capture the health benefits within a clinical trial setting. Given the problematic nature of QALYs in this patient group, health benefits need to be viewed in the round, not just as contributing towards the generation of QALYs. While data and methods can be further explored to improve HRQoL and utility estimates (e.g. extending the case vignette study) in order to determine the most appropriate tool for HRQoL data collection within an MAA, it is argued that the QALY is unlikely to capture all the health benefits associated with nusinersen. From this perspective, the QALY may be intrinsically incapable of fully incorporating the benefits of nusinersen into the estimates of cost-effectiveness. In addition, given the rarity of the condition, data quantifying the true cost to the health and social care systems, to carers and to wider society in the form of lost productivity, are sparse.
21	Paragraph 3.23 noted the committee's assessment that nusinersen for early onset SMA could meet the end-of-life criteria but that, for later onset, it did not. As stated by the committee, blurred boundaries between different types of SMA, the nature of the population and the rarity and severity of SMA, it could be considered unreasonable to apply a different level at which nusinersen would be considered cost-effective depending on the age of onset of SMA, but a conclusion was not reached on this. Biogen agree with the committee that it may be unreasonable to apply different cost-effectiveness criteria depending on the age of onset of SMA and, considering the 60% share of incident cases of SMA accounted for by infantile onset, would suggest that end-of-life criteria should be applied across the board. Further understanding from NICE is sought on the implications of the end-of-life criteria for the ICER that can be considered.
22	Paragraph 3.24 noted that the committee was willing to take into account a range of factors in its decision making, including flexibility in its considerations around uncertainty, particularly if access could be managed so as to reduce the risk to the NHS. However, nusinersen would need to be plausibly within a range that could be considered cost effective. Results of the company and ERG analyses show the extent of the uncertainty in the cost-effectiveness estimates. Collecting further data and gaining a deeper understanding of the impact of SMA on patients and carers is required to improve these estimates. Furthermore, as previously mentioned, Biogen are continuing to develop a proposal for a managed access agreement (MAA) for consideration by the committee in October.

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted

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under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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

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

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Nusinersen for treating spinal muscular atrophy [ID1069]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Muscular Dystrophy UK
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
1	As a charity supporting people being denied treatment for spinal muscular atrophy (SMA), we are extremely disappointed that the committee has rejected nusinersen. This is the first and currently only treatment for people with spinal muscular atrophy, which is a devastating and progressive condition. We appreciate the financial constraints that the NHS has to operate within, however, we also strongly believe that this treatment should be made available to those that would benefit from it, on the basis of clinical decision making, rather than on purely cost-effectiveness grounds. The process of assessing nusinersen in the UK has been lengthy, with over 7 months between European Medicines Agency approval and the start of the NICE appraisal process. It will be at least 18 months since the treatment was approved by the time the NICE process concludes. This is completely unacceptable. During this time, the condition of patients who could benefit from the treatment will have irrevocably altered and it is only because of the Expanded Access Programme that we have not seen many children dying during this period. There is a moral imperative for devastating progressive conditions, like SMA, to be be assessed rapidly. We do not believe that the Single Technology Appraisals route has been an appropriate tool for assessing this treatment and feel it highlights the shortcomings of the existing system in terms of adequately assessing rare disease treatments.
2	Nusinersen has been shown to have positive, potentially life-changing and life-saving results, particularly for children with SMA, a point emphasised by clinicians and recognised by the committee. The treatment has been shown to improve longevity but also motor function, including respiratory function. It also represents a bridge to new emerging treatments for people with SMA. Without access, the condition will be left untreated and people's health and independence will progressively decline.
3	We are concerned that this recommendation could result in children with SMA Type 1 dying when the current Expanded Access Programme is closed in November 2018. If NICE do not change their decision or find an alternative means of granting access (such as a managed access agreement) then we know that babies diagnosed with SMA Type 1 after November 2018 are unlikely to reach their second birthday. In our eyes, this represents a clear moral imperative for the committee to re-evaluate their current stance.

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4	We do not believe that the provisional recommendation constitutes suitable guidance to be implemented by the NHS. We are concerned that the evidence supplied by patients, carers and clinicians on the physical, emotional and practical benefits of nusinersen do not seem to have been given significant weight in the consideration of the evidence.
5	We were pleased to see mention of the possibility of a managed access agreement to address the uncertainties in evidence of long-term benefits highlighted by the committee. However, it was concerning to read that the committee felt the details of the company's proposed managed access arrangement were "vague and currently insufficient for it to assess whether it could be an option." Given the impending closure of the Expanded Access Programme, we strongly believe that NICE, NHS England and the company should work together to secure a managed access arrangement for nusinersen as soon as possible and no later than end of October 2018. Evidence has shown that the treatment is clinically effective and is currently the only treatment available for the condition. If the only uncertainties are around cost and data then these can be addressed via an access agreement whilst ensuring patients can continue to benefit from the treatment.
6	We understand that the evidence currently available suggests that the technology is particularly useful at the earliest stages suggesting it could be more appropriate to prioritise treatment for children at diagnosis and pre-symptomatic children. This relies on early diagnosis. Symptoms for Type 1 are within the first few months of live and sometimes before birth, whereas symptoms for Type 2 and 3 are usually seen from 7-18 months.
7	We strongly believe that "Type" of SMA should not be the determining factor in whether or not a patient receives treatment. There is such a broad spectrum across each type and the boundaries between types can be blurred. For example, some stronger Type 1s currently accessing nusinersen on the Expanded Access Programme are now sitting up - clinically speaking, this would now make them a Type 2.

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
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the person could be identified.

- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Nusinersen for treating spinal muscular atrophy [ID1069]

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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):	[**Spinal Muscular Atrophy Support UK and The SMA Trust**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]

Nusinersen for treating spinal muscular atrophy [ID1069]

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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.

1	**Has all the relevant evidence been taken into account?**
	
	NICE's committee papers: evidence of population with SMA
	
	The evidence suggests that the committee's estimation of the population that would access treatment is too high.
	
	We understand NICE is basing its discussions on the following statement in the summary slide 'Disease Background':
	
	'It is estimated that about 100 people are born with SMA per year in the UK, and currently between 1,200 and 2,500 children and adults with SMA in the UK.
	
	We have been unable to ascertain how NICE has derived its prevalence and incidence data. We note that NICE's figures are similar to estimates we were aware of in 2013 derived as follows:
	
	• At the 2013 SMARTnet /Patient Registry meeting, a lead clinician stated that **there are some 1200 people affected by SMA in the UK at any one time – children and adults**.
	
	• We asked another leading clinician that same year for their calculation which, based on the then estimated incidence of **100 children born with SMA per year**, they gave as follows
	
	  • **Type I**: accounts for 50-60% of all SMA but median life expectancy is 1 year, so rough estimate is that there are about **25** children alive in the UK with Type I at any one time.
	
	  • **Type II**: median life expectancy about 25 years, 25% of all SMA so prevalent

population is 25 x 25 = **625.**

- **Type III**: by the same reasoning 25x70=**1750.**
- **TOTAL approx. 2,500,** but this is the upper limit and the **true figure is probably around 1,500-2,000.**

As there were no other figures available at this time, these figures and calculations became public.

We consider this to be incorrect based on evidence presented in these two recent studies:

- Verhaart I *et al.* (2017) **Prevalence, incidence and carrier frequency of 5q–linked spinal muscular atrophy –a literature review.** *Orphanet J Rare Dis* 12: 124.
- Verhaart I *et al.* (2017) **A multi-source approach to determine SMA incidence and research ready population.** *J Neruol* 264: 1465-1473

These conclude:

I**ncidence**: approximately one in every 10,000 babies worldwide are born with a type of SMA. In England and Wales in 2017, there were 679,106 live births. This suggests that in that year approximately 68 babies were born with a type of 5q SMA.

Prevalence -between 1 and 2 people in every 100,000 worldwide have a type of SMA. In 2017, the population of England and Wales was approximately 58.4 million. Based on this, it is estimated that between 585 and 1170 people living in England and Wales have SMA.

We are aware these papers are based on global observations of incidence and prevalence but until we have an accurate UK wide register of those born with 5q SMA and those living with 5q SMA we ask NICE to use them to guide analysis and decision making.

Population that would seek treatment

From the perspective of NICE's decision making, it is not only important to know the actual population but also to be aware and take into consideration that:

- **Not everyone who has 5q SMA will want treatment**. Reasons cited are:
  - the invasive method of administration and necessary commitment to its long-term repetition
  - the unknown long-term outcomes
  - an awareness there are more treatments, such as gene therapy, on the horizon.

	We remind NICE of our 2018 survey of parents/carers of children and young people with SMA and adults with SMA which we submitted in which: o 18%. of people with SMA (total respondents 56) – most of whom would be adults - said they would not want nusinersen treatment o 5% of parents/carers (total respondents 55) said they would not want nusinersen treatment for the child / young person they care for The same observation applies to both groups in that those not interested in treatment may not have been engaging in the discussion let alone have responded to the survey – in which case the percentage who would not seek treatment may be higher. • **The treatment may not be clinically safe for everyone with SMA** • There has been **no clinical evidence of the treatment for those with SMA Type 0 or 4**. Although the number with these types of SMA are small, again this lowers the likely population that will seek treatment if it is funded by the NHS **In summary: when considering all with 5q SMA, we suggest that an appropriate population base is:** o ***Incidence:*** **1 in every 10,000 – approximately 68 babies born with 5q SMA each year in England and Wales.** o ***Prevalence:*** **between 1 and 2 people in every 100,000 worldwide have a type of SMA - approximating to between 585 and 1170 people living in England and Wales having SMA** **We further suggest that the population that would seek treatment is lower than the prevalent figure:** o **Not everyone who has 5q SMA will want treatment** o **The treatment may not be clinically safe for everyone with SMA** o **There is no clinical evidence of the treatment for those with SMA Type 0 or 4**. **We are concerned that an over estimation of the population who would seek and for whom this treatment would be clinically safe may lead to incorrect assumptions by NICE as to the total budget that would be required**
2	**Has all the relevant evidence been taken into account?** **Consultation Paper 3.5 NICE's Clinical Evidence** We note that NICE only discusses evidence from the published results of the clinical trials ENDEAR and CHERISH. We understand that Biogen will be submitting further evidence

published in 2018.

We would like to be assured that NICE has considered the additional recently published clinical evidence from 'real world' studies. Though the studies were not all conducted in the UK, all the clinical practice is guided by the 2017 internationally agreed Standards of Care for SMA (**Mercuri, E *et al.*** (2017) **Diagnosis and management of spinal muscular atrophy: Part 1: recommendations for diagnosis, rehabilitation, orthopedic and nutritional care.** Neuromuscul Disord. 2018 Feb;28(2):103-115. and **Finkel, R et al** (2017), **Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics**. Neuromuscul Disord. 2018 Mar;28(3):197-207.)

We note that the real-world studies only review outcomes for children with SMA Type 1 for the first six months of treatment but consider 'real world' evidence critical to decision making. They all assist with confirming the certainty of evidence of effectiveness (see below). In particular we refer to:

Reviews of the Expanded Access Programme:

- **Europe -** 33 children aged from 8.3 to 113.1 months - December 2016 - May 2017.
  Aragon-Gawinska, K *et al*. (2018) **Nusinersen in spinal muscular atrophy type 1 patients older than 7 months. A cohort study** Neurology® 2018;00:1-7. doi:10.1212/WNL.0000000000006281

- **Australia** – 16 patients aged 2.5 months to 35.7 years November 2016 – September 2017
  Farrar, M *et al*. (2018) **Nusinersen for SMA: expanded access programme** J Neurol Neurosurg Psychiatry 2018;**89**:937–942. doi:10.1136/jnnp-2017-317412

- **England - Great Ormond Street Hospital** – 21 patients aged 8.3 – 113.1 months March – October 2017
  Tillmann, A *et al.* (2018) **Spinal Muscular Atrophy (SMA) type 1, a changing phenotype: Implications for motor function and physiotherapy management from the Nusinersen Expanded Access Program (EAP)** APCP Journal Volume 9 Number 1

- **Germany** – 61 patients aged 1 – 93 months in seven neuromuscular centres November 2016 – June 2017
  Pechmann, A *et al.* (2018) **Evaluation of Children with SMA Type 1 Under Treatment with Nusinersen within the Expanded Access Program in Germany** Journal of Neuromuscular Diseases 5 (2018) 135-143 DOI 10.3233/JND-180315

	• **Italy** – 104 patients – aged 3 months – 19 years 9 months - first six months of EAP **Pane, M *et al.*** (2018) **Nusinersen in type 1 SMA infants, children and young adults: Preliminary results on motor function** Neuromuscular Disorders 28 (2018) 582-585 30 May 2018 Also: • **Hoy, S** (2018) **Nusinersen: A Review in 5q Spinal Muscular Atrophy** CNS Drugs (2018) 32:689-696 Published online 20 July 2018 © Springer Nature Switzerland AG 2018 **In summary we ask NICE to include in their evidence base the outcomes of 5 'real world' studies of 235 patients age range 1 month – 35.7 years receiving treatment via the global SMA Type 1 Expanded Access Programme.**
3	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** **Consultation Paper 3.6 NICE's conclusion re: clinical effectiveness in terms of survival and improved motor function.** We note **Hoy's overview** (cited above) which supports NICE's conclusion. 'Results from an expanded access programme support the efficacy of nusinersen in the real-world setting.'
4	**Is the summary of clinical effectiveness a reasonable interpretation of the evidence?** **Consultation Paper 3.7. NICE's discussion of other health benefits for early onset SMA**. This focuses on discussion of outcome measures used in the trials. It acknowledges the patient experts view of these 'other' valuable benefits and the importance of any stabilisation and even small improvements in symptoms, especially improvements in motor function. **Aragon-Gawinska, K *et al.*** confirm this and describes parental reports of the wider impacts, impacts that are significant for quality of life: 'It should be noted that many parents reported improvements during treatment with nusinersen that were not captured by the measures used and that were not predefined in data collection such as louder voice, better endurance, and more efficient coughing. Better definition of these outcomes might be useful for long-term follow-up of these patients.'

Pechmann, A *et al.* also note in their study, 'Further research is needed to evaluate the impact of changes in CHOP INTEND score on daily life and on quality of life in children with SMA type 1, which are not as obvious as changes in motor milestones.'

Aragon-Gawinska, K *et a*l. confirm NICE's conclusions when they state:

'Our results are in line with the phase 3 study for nusinersen in patients with SMA1 treated before 7 months of age and indicate that patients benefit from nusinersen even at a later stage of the disease.'

And

'Despite its limitations, this study provides Class IV evidence that nusinersen is beneficial for patients with SMA1 between 7 and 113 months of age.'

ENDEAR's respiratory function, time on ventilator and hospitalisations evidence is currently in confidence and therefore not discussed in NICE's conclusions. With regard to this, though not 'clinical evidence' and already submitted, we remind the committee of the results of our own survey in the UK when we heard from 29 parents whose children had received nusinersen treatment, many of whom had had this for longer than six months:

- **Numbers:** Type 1 - 19; Type 1 / 2 - 9; Type 2 - 2; Type 3 – 1.
- **Age range:** <7 months – 9+ years.
- **Treatment duration**: 0-4 injections – 8; 5-7 injections – 18; 11+ injections -1).

The % reports from 20 parents giving open comments of their observed outcomes of their treated child was as follows:

- Physical / muscle improvements 95%
- Much happier 40%
- Respiratory gains 35%
- General improvement in health 20%
- Increased vocalisation 10%

Typical quotes, taken from the qualitative part of our study, that **highlight the impact of the motor milestones on daily living** are:

'Practically she is able to perform more tasks herself and gained strength to use her own wheelchair.' **Type1, treatment started age 13 - 24 months, 5-7 injections**

Typical quotes that **highlight the gains are not just with mobility and suggest an impact on**

	respiratory function are: 'He has been managing colds all through winter at home whereas before he was in intensive care on life support for every cold he got. He is a happy boy who can now start to explore his surroundings, he is also beginning to talk and can say Mum and dad and can sing and clap.' **Type 1, treatment started < 7 months, 5-7 injections** 'My child required/relied on bipap before treatment and her lungs were getting worse and worse. ….However, nusinersen has stabilised / improved her breathing. She now only requires bipap for sleep and her settings have been turned down following sleep studies.' **Type 1 treatment started 13-24 months, 5-7 injections** 'He can tolerate sitting up for hours without any respiratory support…..Respiratory wise he has gone from being ventilated 22 hours a day to 16 hours a day.' **Type 1, treatment started <7months, 11+ injections** 'Her biggest joy is being able to cough better, and deal with mucus plugs without so much chest physio and cough assist. Also, previously every illness (respiratory or gastric) meant non-reversible deterioration, and now she bounces back almost to the same level as before the illness.' **Type 1 / 2, treatment started 37 months +, 5-7 injections** **In summary: we are pleased to see NICE recognising that any improvements would be highly valued by patients and that it provides important health benefits for early-onset SMA. We suggest that real world studies that comment on parent views and our own survey indicate less uncertainty than NICE concludes.**
5	**Is the summary of clinical effectiveness a reasonable interpretation of the evidence?** **Consultation Paper 3.8 Nusinersen substantially improves motor function for people with later-onset SMA** We note and agree with this conclusion. The real-world studies (see 2) of patients with SMA Type 1 aged I month to 35.7 years indicate, as summarised by **Pechmann, A *et a.l*** that, 'Although this study does not provide evidence comparable to a randomized controlled trial, the results indicate that even in advance stages of the disease, nusinersen can lead to improvement of motor function as measured by CHOP INTEND'. Given these real-world studies have necessarily been restricted to delivery to those with SMA Type 1 the most severe form of SMA, it may not be unreasonable to suggest, as shown in CHERISH that these findings will be at the very least replicated with SMA Type 2 and 3 with all the very positive implications of such outcomes. We also remind NICE that this conclusion was confirmed in our submission which drew

	attention to the very positive outcomes of treatment, not just in terms of motor function, for **a teenager with SMA Type 3** and the impact that the gains have had on all aspect of his daily living. We understand his treatment has continued and this parent will be giving NICE a further update on progress.
6	**Is the summary of cost effectiveness a reasonable interpretation of the evidence?** **Consultation Paper 3.10 Transition probabilities based on assessment of motor milestones** We agree with the Evidence Review Group (ERG) comments that the model structure fails to take account of other key factors affecting health-related quality of life such as; participating in activities, respiratory function, pain and physical impairment. We note that the committee concluded that the models had limitations but were nevertheless suitable for decision making as they were consistent with the main outcomes of the clinical trials. We are not confident that we agree with this conclusion because it is questionable whether the main outcomes were an adequate reflection of the effectiveness of treatment. In **Ethical Challenges Confronted When Providing Nusinersen Treatment for Spinal Muscular Atrophy** Journal of American Medical Association Feb 2018 Volume 172 Number 2**, Burgart, A.M *et al.*** comment on the motor milestone measurements used in the trials as follows: 'Maintaining the most marginal function may be the key quality of life indicator for a patient seeking nusinersen treatment. The measurements used during the trials, while sufficient for patients who met study criteria, may not be sensitive enough to detect minute differences in strength maintained or gained.' Additionally, as shown above (see 4), the range of outcomes measured was limited and did not adequately show their breadth.
7	**Is the summary of cost effectiveness a reasonable interpretation of the evidence?** **Consultation Paper 3.13 Utility values in the economic model are highly uncertain**

We agree with NICE's concerns that identifying robust utility values in babies and young children is exceptionally challenging and draw attention to the flaws the measures present as summarised by **Griebsch, I *et al*. Quality-Adjusted Life-Years Lack Quality in Pediatric Care: A Critical Review of Published Cost-Utility Studies in Child Health** Pediatrics May 2005, VOLUME 115 / ISSUE 5 summarises the issues that this measurement brings:

- Children undergo dramatic changes in growth and function (e.g., mobility, self-care) at different rates, difficulties may arise to attribute improvements to health care interventions rather than to normal development. There is no methodologic guidance about how this should or even might be dealt with.

- All current generic measures (with the exception of the Health Utility Index Mark 2) are derived from adult populations, and additional attributes that are particularly relevant to child health, including, for example, autonomy, body image, cognitive skills, and family relationships, may not be captured by these measures. Furthermore, no generic instrument for children and infants **younger than 5 years** is available.

- Children, particularly young children do not have the cognitive ability to comprehend and complete valuation or even measurement tasks. The implication is that, for very young children, some form of proxy inevitably will be used for measurement tasks, whether this be the clinician or the parent. Although parents may be perceived by economists as the more appropriate source of measurement and/or valuation, the potential for interaction between the utility function of the parent and the proxy (their child) for whom he or she is making the measurement/valuation may lead researchers to choose to use clinician judgment to avoid this problem. The issues with this are that: clinicians only see and record a 'snapshot' which may not truly represent the changes taking place and impact on daily living for both child and parents; measurement tools are insufficiently subtle and limited in their measurements.

This last point is confirmed by the above comments (see 4) and the many studies that show this, for example, **Srikrishna S, *et al.*(**2009*)* **Is there a discrepancy between patient and physician quality of life assessment?** Neurourol Urodyn. 2009;28(3):179-82. doi: 10.1002/nau.20634.

In summary: we agree that both the company and the ERG approaches had serious limitations. We understand NICE's decision to use both approaches sought to address this, but are concerned that the final values may not appropriately reflect the impact of the worst health states caused by untreated SMA as reported in clinical and patient

	expert evidence.
8	**Is the summary of cost effectiveness a reasonable interpretation of the evidence?** **Consultation Paper 3.14 Carer disutilities** We note NICE concluded that quantifying carer -related disutilities was extremely difficult and that the committee was concerned that the proposed model resulted in the counter-intuitive outcome whereby, 'the largest carer disutility was seen in the best health state. We agree with this concern and remind NICE of our survey in which 56 people with SMA, 55 parents/carers and 21 relatives described the huge 'carer burden' of the untreated condition on their lives. In contrast, in 'open comments', 20 families with children still at early stages of treatment described the beginning of the reduction of this 'burden' in the following ways: • Given hope 65% • Emotionally positive and happier 40% • Decreased care needs 20% One family summarised the pre and post treatment change in 'burden' as follows: 'When your child is unstable and having frequent hospital / ambulance admissions this is very draining both physically and emotionally on the whole family. We are more relaxed and able to enjoy day to day life and activities so much more now. SMA is very tough on you as a carer / sibling, but with his stability and health being so much better we feel a lot more happy as a family.' **Type 1, treatment started <7months, 11+ injections**
9	**Is the summary of cost effectiveness a reasonable interpretation of the evidence?** **Consultation Paper 3.15 The ICER is uncertain** **Consultation Paper 3.18 Uncaptured health benefits** We agree with NICE that there is uncertainty and acknowledge the committee's efforts to address flaws in the models in its conclusions. We note that the paper states 'It was not presented with any data to show other distinct and substantial benefits of nusinersen that have not been captured in the economic analysis. We acknowledge that our submission data was qualitative and anecdotal, but it was directly from members of the UK SMA community. We therefore seek an assurance that the economic analysis covered all direct health and personal health and social services costs

	and reflect the observations submitted in our survey results, namely: • **mental health:** o 56% of 132 of 'untreated' respondents reported the person with SMA did not have enough support and intervention to keep emotionally well o 54% of 132 of 'untreated' respondents reported the person with SMA did not have enough support and intervention to get enough sleep o 67% of 132 of 'untreated' respondents reported the main carer did not have enough support and intervention to keep emotionally well o 73% of 132 of 'untreated' respondents reported the main carer did not have enough support and intervention to get enough sleep • **equipment costs and housing adaptations**: o our survey detailed the huge range required • **emergency hospital stays, surgery and clinic time:** o again, these events and related costs are enormous • **continuing health care (CHC) cost:** o these can be significant and, combined with social care / personal budget, up to 24 hour Though we accept there is uncertainty as to future long-term outcomes for those treated with nusinersen, the evidence to date clearly indicates that these wider costs will potentially reduce significantly. We would like assurance that this potential is adequately reflected in the ICER. We also seek assurance that the model reflected that the health impact is not on **one** carer but on many e.g. grandparents who also often play a key role. Also that due to the 'carer burden' of caring for someone with SMA, that it impacts on other caring responsibilities of the carer. In our survey: • 32% of 128 respondents reported the carer had caring responsibilities for **ageing parents** – with the potential that they would not be able to give those parents the care they will need and that these costs will therefore fall to health and social services • 51% had caring responsibilities for **other children** with some reporting that their focus

	on the child with SMA and their needs was impacting negatively on siblings' mental health and behaviour with potential health related costs We are concerned that however much effort NICE has made to adjust the ICER's to better reflect the evidence presented and address shortcomings that do not reflect 'real-world patient expert reports, the appraisal system remains fundamentally flawed. From our perspective there needs to be a much more holistic inter-departmental approach to assessing the costs and benefits of treatment. Only then can the ICERs really begin to reflect the true potential value of this treatment. As examples of this, SMA impacts on: • **education costs**: requiring Teaching Assistants, school adaptations, University PAs • **work costs:** carers (parents and grandparents) and patient – loss of potential productivity and contribution to the economy through work / taxes. In our survey: o 52% of 132 respondents reported that the interventions and support they have is not enough for the person with SMA to work / study for the hours they wish o 70% of 132 respondents reported they were not enough for the carer to work / study for the hours they wish • **health and social care costs borne by families:** o 45% of 132 respondents reported that the interventions and support the person with SMA and their carers have are not enough for that person to manage financially o 60% of 132 respondents reported that they are not enough for the carer to manage financially • **equipment and housing adaptation costs borne by families:** Examples from our survey of items that many respondents reported were not NHS funded: o 71% of those using a wizzybug o 70% of those needing a specialist car seat o 57% of those needing a wheelchair accessible vehicle o 52% of those who had needed home adaptations o 50% of those needing a powered wheelchair

	o 50% of those requiring assistive technology **SMA is a progressive condition which mean these costs increase over time. Treatment that results in stability alone can result in a huge reduction in these costs.** **In summary: we seek an assurance that the economic analysis covered all the real-world costs of all the health and personal health and social services required to support a person with SMA and their family and included the impact of SMA affecting more than one carer. We also wish it to be noted that we consider the model falls short in that it fails to cover the real-world costs that lie outside the realm of health and social services. We are aware this is not possible within this appraisal but consider that this needs to be urgently addressed by NICE.**
10	**Are the provisional recommendations a sound and suitable basis for guidance to the NHS?** **Consultation paper 3.16.** states 'Although the committee recognised that a managed access arrangement could reduce the risk to the NHS, the ICER for nusinersen would need **to plausibly be within a range that could be considered cost effective**, and it would require NHS England, patients, carers and clinicians to sign up to it. **Due to nusinersen having been assessed via a Single Technology Appraisal (STA), we consider the ICER threshold is inappropriate and urge flexibility when establishing what will be an appropriate range.**
11	**Are the provisional recommendations a sound and suitable basis for guidance to the NHS?** **Consultation Paper 3.20** We note NICE's statement that its decision to appraise the treatment via an STA rather than via a Highly Specialised Technology (HST) was 'because the population covered by the marketing authorisation is larger than that which can be considered in HST evaluations'. We refer back to our previous comments (See 1) highlighting our concern about the figures used by NICE to draw this conclusion. We also wish to draw attention to the thresholds comparable regulatory bodies use for considering rare orphan / ultra orphan medicines: • **Scotland** is introducing a new definition of 'ultra-orphan medicines' that can treat very rare conditions affecting fewer than 1 in 50,000 people - around 100 people or less in Scotland. This will include SMA and allows the Scottish Medicines Consortium (SMC) the

ability to treat some medicines for rare orphan diseases as ultra-orphan medicines. www.news.gov.scot/news/treatments-for-rare-conditions

- **The European Medicines Agency** states that for orphan designation, the **prevalence** of the condition in the EU must not be more than 5 in 10,000 (1 in 2,000) or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development;

Though it is not clear what population threshold NICE uses given its HST guidance (August 2018) now states that for a topic to be selected, 'the target patient group for the technology in its licensed indication' has to be 'so small that treatment will usually be concentrated in very few centres in the NHS' we understand that previously **NICE's commonly accepted threshold** for considering scoping a treatment as an HST was, that it would be accessed by fewer than 500 patients in England and Wales. If this were the case this would be the equivalent of **1 in 110,000 (Population for England and Wales 2017).** If the threshold moved in line with Scotland it would in contrast, include **1,313 patients.** As outlined in (1) above, the total target population would come well within this.

We also note that the treatment was excluded from being appraised via an HST because it is 'not commissioned through a highly specialised service.' We question how appropriate such a barrier to HST appraisal is for a condition such as SMA which is clearly rare but for which, for safe and efficient delivery, treatment needs to be delivered as close to a person's home as possible.

We note that Biogen's EAP, which has given the drug free has been opened in both highly specialised and specialised centres in response to strong advocacy from patient groups and clinicians which highlighted:

- A need to circumvent a postcode lottery
- The need for children not to travel (health risks, burden on families)
- The capacity issues of centres that were open.

In view of this, we consider this range of centres is an appropriate response to the treatment needs of this population. It is a credit to Biogen that they agreed to provide the drug to a wide number of centres and that as a result, more than 80 children are having treatment in across the UK. In so doing we imagine Biogen was aware that this very move would offer one more reason to push the drug out of the HST appraisal route into that of an STA for common diseases.

We understand that this treatment did not meet 4/7 of the HST topic selection criteria (Sir David Haslam letter to clinicians 3 September 2018). As such it has missed out on being assessed against the higher HST ICER threshold and has instead been assessed as an STA for

	common diseases. We strongly contest that this is an inappropriate threshold and that the choice of only these two routes has created undue delays and difficulties with the assessment of this treatment and condition. This has meant that, despite the clinical evidence available, there has been no access for anyone other than those with Type 1 < 7 months of age. In contrast, in July 2018 Biogen reported 20 European countries had access to nusinersen via routine reimbursement. We have provided information and emotional support to one family already who has chosen to move to one of these countries as they are desperate to access treatment. This is not a choice they wanted to make and has been a hugely complex and distressing decision. We know of other vulnerable families also feeling forced to consider this. This is only going to get worse with the imminent closure of the EAP for Type 1 on 1st November. If not resolved before then we will see infants with SMA Type 1 missing the critical early treatment window which gives the best opportunity for positive outcomes and the very real prospect of these infants dying. **In summary: We urge NICE to:** • **Take account of the STA presenting what we regard as an inappropriately low ICER threshold for this treatment and reflect this in a more flexible approach to an agreed higher price threshold within a timely Managed Access Agreement (MAA).** • **Ensure that England and Wales offer access in line with Europe**
12	**Are the provisional recommendations a sound and suitable basis for guidance to the NHS?** **Consultation Paper 3.23** We agree with the committee that 'it could be unreasonable to apply a different level at which nusinersen would be considered cost effective depending on age of onset of SMA'
13	**Are the provisional recommendations a sound and suitable basis for guidance to the NHS?** **Consultation Paper 3.24** We acknowledge the committee's comment, 'The very high cost of nusinersen means that there is a significant financial risk to the NHS if the committee were to recommend a technology for routine that may not be cost effective' However we point out that many families have expressed that they see this treatment as a vital bridge to further new treatments which are coming close to completion of clinical trials and, one imagines possible applications for licences (**AveXis' AVXS-101, Roche's RG7916 / risdiplam**). In the light of this, we ask the committee to consider that this risk may not be very long term.

	We were also pleased to read the committee is, 'Willing to be flexible around uncertainty, particularly if access could be managed such that risk to the NHS was reduced' and consider it possible, via a Managed Access Agreement, to collect data that will reduce uncertainty. We suggest collection of the data could include reviewing and incorporating the work of **Chad Heatwole, MD,** at the University of Rochester, who, in his project, " Development of a Clinically Relevant Outcome Measure for Pediatric SMA Therapeutic Trials." is working to develop SMA-specific patient reported outcome measures for use in SMA clinical trials and clinics. One such instrument, the Spinal Muscular Atrophy Health Index (SMA-HI), was developed and validated using FDA guidelines for SMA patients age 8 to 85. This instrument is currently being utilized to measure therapeutic response in clinical trials. The new work will look at developing properly validated, disease-specific, observer-reported outcome measure for infants and children (under 8 years of age) with SMA.
14	**May the preliminary recommendations need changing because they could have an adverse impact on people with a particular disability or disabilities?** We would argue 'yes', most definitely this decision has an adverse impact on all with SMA who would have wanted and for whom it would have been clinically safe to access the treatment. This decision deprives these people of the possibility of accessing a life-changing treatment that has the potential to have a huge impact on both their quality of life and the quality of life of their families.
15	**Is there a clinically distinct subgroup of people in whom nusinersen is expected to be more clinically effective? How could this group be identified in clinical practice?** We note that the cost of the drug is covered by Biogen's EAP for all those currently living with SMA Type 1 (prevalent population). We assume that NHS England's 9 March 2018 commitment to cover the costs of administration of the drug remains in place. We note that there is no clinical evidence for treatment of those with SMA Type 0 and Type 4 We suggest that there are **three groups** all of whom are **of equal importance** and for all of

whom there is potential for clinical effectiveness. They are differentiated only so that different 'work streams' can be established within any MAA:

Group A

Clinical evidence (ENDEAR and CHERISH Trials) and 'real-world' studies cited above indicate that early treatment provides greater effect. This includes those with Type 1, 2 and 3 where it is clinically safe, and the clinicians and family agree on treatment. Note that, for a range of (personal) reasons, not all will want treatment. For example, **Farrar, M *et al.*** cite, that 4 of 20 families with children eligible for treatment chose not to go ahead. It is a very individual decision requiring informed consent.

- **How could this group be identified in clinical practice?**

We suggest this group could be easily identified at the time of diagnosis and that for England in any one year, given the incidence (see references and calculations in 1) is likely to be **68 children** including those diagnosed with:

- Type 1: 60% - 41 infants age < 6 months
- Type 2: 21% - 14 children ages 6 – 18 months
- Type 3: 19% - 13 children including
    - Type 3a ages 18months – 3 years
    - Type 3b age 3 years plus

Though outside the scope of this appraisal, we note and agree with the comments made by **Farrar, M *et al.*** (2018) **Nusinersen for SMA: expanded access programme** J Neurol Neurosurg Psychiatry 2018;**89**:937–942. doi:10.1136/jnnp-2017-317412

'that further education of healthcare professionals seeing infants at risk of SMA type 1 is necessary.'

And that 'Newborn screening (NBS) presents as the best opportunity to considerably reduce medical morbidity resulting from a delayed diagnosis of SMA type 1' and indeed the impact of other types of SMA.

We note that the UK national screening consultation for SMA is currently calling for

comment as to whether criteria for this to be recommended have now been met. One of these is that a viable treatment is available. This relies on a positive recommendation by NICE, at which point there could be the potential for even earlier treatment for these 68 infants each year.

We are aware that there are sensitive considerations around the ethics of screening for a condition when the potential impact varies greatly, and the treatment delivery is invasive and requires a long-term commitment but understand that the screening consultation will be addressing potential issues.

We note that several US states have recently introduced newborn screening and those with between 1 and 3 *SMN2* copies are offered treatment. However, we note from the internationally agreed Standards of Care the variance between the 'usual' number of *SMN2* copy numbers compared with the possible 'range' (**Tillmann, A *et al.***):

- Type 2 have a 'usual' *SMN2* copy number of 2 but a 'range' of 2-4 copies
- Type 3a have a 'usual' *SMN2* copy number of 3 but a 'range' of 3 – 5 copies
- Type 3b have a 'usual' *SMN2* copy number of 4 but a 'range' of 3 – 5 copies

As stated in the International Standards of Care, at the individual level, perfectly accurate predictions cannot be made about the type or severity of SMA based on the *SMN2* copy number alone. This is likely to be because other genetic and possibly environmental factors have an influence on the disease. Added to this there can be delays in obtaining *SMN2* copy number results which, for this group may impact on what is a critical window for intervention.

Group B

We note Biogen's clinical results (CHERISH Trial) and now the SHINE study. We also note the real world studies of those with SMA Type 1including recent publication of the study by **Aragon-Gawinska, K *et al.*** which commented, 'new motor acquisitions were attained even in 8-year-old patients' and **Pane, M *et al***. whose treatment of those with SMA Type 1 included people in the age range 3 months to 19 years, 9 months with 95 of the 104 older than 7 months, 'Our results suggest that some therapeutic efficacy is possible even after the first seven months even if the consistency or the magnitude of response was variable and often smaller than those observed with early intervention.'

This returns us to the point that stability alone can make a significant difference to quality of life and reducing the true costs of the condition for the individual, their families and

caregivers and health and social services (see 9 above).

We therefore consider that access is **of equal importance** for all with Type 2 and 3 where it is clinically safe, who are at a **critical point** and the medical team and family/adult agree treatment offers a potential benefit.

The need for treatment access for this group is discussed in **Burgart, A *et al's*** article which gives examples of:

'older patients with advanced SMA may be clinically stable in terms of vital physiological functions but on the verge of losing a key functional ability, such as communicating by computer or operating adaptive equipment'. Achieving stability is critical

Other examples might be a child whose scoliosis is progressing significantly or, as there is a tendency for children to become weaker at times of major growth spurts such as puberty, children who are reaching this stage.

An outcome that maintains stability would be sufficient reason to continue treatment.

Not all in this group will want treatment. It is a very individual decision requiring informed consent.

- **How could this group be identified in clinical practice?**

There would perhaps need to be agreement by a clinical / patient group as to guidelines for what constitutes a 'critical point' and perhaps an overarching national 'appeals group' to ensure equity. If used, as **Burgart, A *et al.*** point out, this would need to 'incorporate appropriate stakeholders, including patient advocates, clinicians, community members, ethicists, and others'

We suggest, that though we are aware this is a workload for already pressured clinicians, immediate work is undertaken by a group such as the NorthStar network group and also by clinicians who care for adults with SMA Type 2 and 3. This would be to review caseloads and prepare very brief details of anyone with SMA Type 2 or 3 whom they consider would meet agreed 'critical point criteria' so that numbers and geographical location can be ascertained.

If helpful, SMA Support UK could endeavour to assist with identification of this group by contacting the community as we did when we worked with NHS England to trying to

	establish how many families with children with SMA Type 1 wanted access to the EAP. The UK SMA Patient Registry would be another potential source of assistance – with all working together. Without this preliminary work being undertaken as a matter of urgency, we cannot know the size of this group. **Group C** This group, **of equal importance,** is all those with Type 2 and 3 who are not at a critical point, where it is clinically safe, and the medical team and family/adult agree that treatment has potential to bring stability. We note again the findings of CHERISH and now SHINE and real-world studies that have included older patients with SMA Type 1 to positive effect. Treatment of this group will potentially bring benefits in delaying or preventing individuals reaching the 'critical' point of Group B. These benefits would impact positively on both quality of life and the true costs of the condition for the individual, their families and caregivers and health and social services (see previous points) • **How could this group be identified in clinical practice?** We suggest a similar exercise to the above. SMA Support UK could help gather this information as could the UK SMA Patient Registry – with all working together. Again, not everyone will want this treatment. It is a very individual decision requiring informed consent. There are adults and young people who won't want this treatment and would rather wait for one with a less invasive delivery. **In summary we identify three clinical sub groups all of whom can be identified in clinical practice. They are all of equal importance as clinical evidence demonstrates they all have the potential of benefiting from treatment. They are differentiated only so that different 'work streams' can be established within any MAA. They are:** • **Group A: all newly diagnosed with SMA Type 1, 2 or 3** • **Group B: all with Type 2 or 3 who are at a 'critical point' in terms of the progressions of their SMA**

	• **Group C: all with Type 2 and 3 who are not at a critical point but where treatment will potentially bring stability**
16	**Is there a clinically distinct subgroup of people in whom nusinersen is expected to be more clinically effective? How could this group be identified in clinical practice?** **The logistical challenges of providing treatment** We are very aware that Centres are limited as to how many people they can manage to treat and, as noted by **Burgart, A *et al.***, the need for, 'high-level operational planning and coordination.' Their further comments about the need for different workstreams to meet needs could fit well with our suggested groupings: 'The task of administering the medication consists of at least 3 clinical work flows: the first involves patients for whom lumbar puncture administration is relatively straightforward and can be performed in an outpatient clinic visit, the second involves patients who require a higher level of supportive care to safely undergo the procedure and fully recover to return home, and the third involves patients who are already hospitalized or those whose clinical condition requires recovery in the hospital. These workflows do not necessarily compete with each other for resources, so that patients queued in one work flow are not necessarily ahead of or behind patients queued in another workflow'. **In summary: The EAP has ensured that many paediatric centres are ready and delivering treatment. We don't know how ready adult services are to respond to new work streams. Any exercise to collate numbers for treatment must map out location of patients and a plan for ensuring efficient delivery and geographical equity.**
17	**Is there a clinically distinct subgroup of people in whom nusinersen is expected to be more clinically effective? How could this group be identified in clinical practice?** **Including all, and allowing for new developments with delivery methods** We note the many developments in delivery for those with spinal scoliosis / who have had spinal surgery as follows:

- **Germany** – 26 patients

Mousa, M *et al.* (2018) **A comprehensive institutional overview of intrathecal nusinersen injections for spinal muscular atrophy** # Springer-Verlag GmbH Germany, Springer Nature July 2018

'Although we achieved 100% technical success in intrathecal nusinersen administration, our practices evolved during the course of this study. As a result of our early experience we developed an algorithm to assist in promoting safe and effective nusinersen administration in children with spinal muscular atrophy regardless of SMA type, abnormal spinal anatomy and complex spinal instrumentation.'

- **USA** – 3 patients ages 12 – 17 years

Veerapandiyan, A *et al.* (2018) **Cervical puncture to deliver nusinersen in patients with spinal muscular atrophy** Neurology® 2018;91:e620-e624.

'Cervical puncture is a feasible alternative delivery route to administer intrathecal nusinersen in patients with longstanding SMA and spine anatomy precluding lumbar access when done by providers with expertise in this procedure'.

- **Germany** – 4 children

Weaver, J *et al.* (2017) **Transforaminal intrathecal delivery of nusinersen using cone-beam computed tomography for children with spinal muscular atrophy and extensive surgical instrumentation: early results of technical success and safety** Pediatr Radiol (2018) 48:392-397

'Cone-beam CT guidance with two-axis navigational overlay is a safe, effective method for gaining transforaminal intrathecal access in children with spinal abnormalities and hardware precluding the use of standard techniques.'

- **Germany** – 20 children

Strauss, K *et al.* (2018) **Preliminary Safety and Tolerability of a Novel Subcutaneous Intrathecal Catheter System for Repeated Outpatient Dosing of Nusinersen to Children and Adults With Spinal Muscular Atrophy** J Pediatr Orthop 2018; 00:000–000

'In summary, nusinersen via repeated intrathecal injection is effective therapy for all types of SMA, but its standard method of interlaminar delivery poses both absolute and relative challenges for a large proportion of patients. More data are needed to determine if nusinersen has comparable efficacy when delivered by subcutaneous port as compared with the standard interlaminar route. However, our initial observations are promising, and long-term administration of nusinersen via the SIC or similar device has the potential to double the number of children worldwide who can safely receive the drug while simultaneously lowering its long-term administration cost 5- to 10-fold.'

	'Although the SIC was designed for SMA patients with advanced disease and attendant spinal pathology, our preliminary observations have implications for younger, less severely affected patients. As private and government insurers adapt to the extraordinary costs associated with new disease-modifying precision therapies, they will likely seek practical innovations like the SIC, which have the potential to safely control administration costs while preserving therapeutic value.' **In summary: we urge NICE to ensure that people whose SMA has created challenges in terms of the delivery of the drug are also given the opportunity to discuss the possibility with their clinicians. The ability of clinicians to explore and implement these options in the UK could lead to new methods of delivery and reduction in costs of delivery.**
18	**In summary:** • We are concerned that NICE's apparent over estimation of the population who would want this treatment and for whom it would be clinically safe may lead to incorrect assumptions by NICE as to the total budget that would be required • We ask NICE to include in their evidence base the outcomes of 5 'real-world' studies of 235 patients aged 1 month – 35.7 years receiving treatment via the SMA Type 1 Expanded Access Programme. • We suggest that real world studies that comment on parent views and our own survey indicate less uncertainty about treatment outcomes than NICE concludes • We agree with NICE that both the company's and the ERG's approaches to economic models had serious limitations. We understand NICE's decision to use both approaches sought to address this, but are concerned that the final ICER values may not appropriately reflect the impact of the worst health states caused by untreated SMA as reported in clinical and patient expert evidence • We seek an assurance that NICE's economic analysis covered all the real-world costs of the health and personal health and social services required to support a person with SMA and their family and included the impact of SMA affecting more than one carer. We also wish it to be noted that we consider the model falls short in that it fails to cover the real-world costs that lie outside the realm of health and social services. We are aware this is not possible within this appraisal but consider that this needs to be urgently addressed by NICE • We contend that due to nusinersen having been assessed via an STA, the ICER threshold is inappropriate and urge flexibility when establishing what will be an appropriate range for a Managed Access Agreement.

	• We urge NICE to ensure that England and Wales offer access in line with Europe and that there is no break in the delivery of treatment to infants with SMA Type 1 once Biogen's EAP closes on 1st November
	
	• We identify three clinical sub groups all of whom can be identified in clinical practice. They are all of equal importance as clinical evidence demonstrates they all have the potential of benefiting from treatment. They are differentiated only so that different 'work streams' can be established within any MAA. They are:
	
	  • Group A: all newly diagnosed with SMA Type 1, 2 or 3
	
	  • Group B: all with Type 2 or 3 who are at a 'critical point' in terms of the progressions of their SMA
	
	  • Group C: all with Type 2 and 3 who are not at a critical point but where treatment will potentially bring stability
	• The EAP has ensured that many paediatric centres are ready and delivering treatment. We don't know how ready adult services are to respond to new work streams. Any exercise to collate numbers for treatment must map out location of patients and a plan for ensuring efficient delivery of treatment to all three groups and geographical equity.
	
	• We urge NICE to ensure that people whose SMA has created challenges in terms of the delivery of the drug are also given the opportunity to discuss the possibility of treatment with their clinicians. The ability of clinicians to explore and implement these options in the UK could lead to new methods of delivery and reduction in costs of delivery.
	
	• We are concerned that NICE's appraisal system has led to undue delays and difficulties resulting in England and Wales being almost the only countries in Europe not offering access to what is proving to be an effective treatment for so many with this devastating condition.
	
	• We urge NICE to continue to meet with NHS England, Biogen, clinicians and patient groups to agree a Managed Access Agreement with work streams that will provide access to all with SMA Type 1, 2, and 3 whom we have identified in this response.

Insert extra rows as needed

Nusinersen for treating spinal muscular atrophy [ID1069]

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The first serious concern with the draft recommendation is that it seems to restrict itself to the RCT data while ignoring the available real-world evidence (RWE) generated in post-MA clinical use of the drug. In case of clinical research in phenotypically varied ultra-rare disorders like SMA, where RCT data cannot reasonably cover all the disease manifestations, it crucial that all available evidence is considered whilst appraising the intervention authorised in treatment of the entire spectrum of the disorder, consistently with the drug's label. RWE evidence on nusinersen effects across the SMA spectrum, which is increasingly being published in academic journals, is largely supportive of the RCT results, even as it additionally covers other populations. TreatSMA has made it available to the Committee at the consultation stage. In particular, the committee had received studies on long-term effect of nusinersen treatment in patients classified as SMA type 1 older than 6 months. The Committee was also briefed about the real-life benefits of nusinersen treatment in presymptomatic and early symptomatic patients. Furthermore, the clinical experts have highlighted to the Committee during the initial appraisal meeting that their observations indeed correlate to evidence reported by caregivers. For instance, since the 2017 start of the nusinersen expanded access programme at the Great Ormond Street Hospital in children with the most severe form of SMA, not a single child has passed away, for the first time in the hospital's history. We need to note that a recent class-IV evidence by Aragon-Gawinska *et al*, who analysed nusinersen efficacy in post-MA setting in a sample of 33 SMA type 1 patients aged 8 to 113 months, concludes that the functional improvement due to treatment was unrelated to their age at start of treatment or the number of *SMN2* copies (doi: 10.1212/WNL.0000000000006281). We at TreatSMA have anecdotal evidence of similar nusinersen efficacy in 6 adult patients with symptoms consistent with borderline SMA type 1 and 2 phenotype, with an increase of several HINE points ([redacted]) over 6 months of nusinersen treatment. We find this apparent disregard to RWE puzzling, especially considering the rarity of the disorder and the challenges related to generating data across the entire phenotypic spectrum of this monogenic disease. Increasingly, HTA agencies worldwide attach significant weight to RWE, considering it a better predictor of the treatment's effects in clinical practice. In many cases, high-quality RWE is regarded on a par with RCT evidence (several meta-analyses of HTA practice in various countries are available in academic journals). Thus, we suggest that the Committee reviews the draft ACD in consideration of all the available evidence, including in particular published and unpublished data from global clinical practice.
2	We are concerned that the negative recommendation seems to rely predominantly on the uncertainty of long-term effects of treatment, in an apparent disregard for the pathological mechanism of spinal muscular atrophy and the molecular mechanism of action of nusinersen intervention. The drug, as evidenced in clinical studies, increases the amount of cell-available SMN protein through modifying the splicing of the SMN2 gene, thus addressing the root cause of SMA pathology (i.e., the deficiency of the SMN protein in motor neuron cells). There is no plausible, scientific reason to speculate that the SMN2-targeting action of this antisense oligonucleotide could stop at one point. Contrary: long-term observations confirm that nearly all

	patients in whom the drug has been effective continue improving over years, albeit, naturally, in a variable degree. The short span of the observations in the two phase-III clinical trials did not always show major milestone achievement over the trial duration, however long-term data, including self-reported data, offer no doubt that improvement continues. While long-term data is yet to be generated, as is the case with every new drug, we stress that in view of the drug's mechanism there is no sane reason to doubt that treatment will offer increasing benefits to patients over time.
3	We are concerned that the model inadequately estimates the disease burden for UK patients and their carers, which in turn likely translates into incorrect estimation of disease state disutilities. The patient and carer health state estimation appears to have been based exclusively on a single study with data collected predominantly in Spain (Bastida et al), a country with an entirely different social care system and significantly lower associated costs; data from other countries than Spain in that study is of low quality and should be avoided in pharmacoeconomic analyses. Rough calculations carried out by TreatSMA and based on data sourced from the UK families suggest that an average disease-related financial burden ranges from around £80,000 a year in SMA type 2-3 to more than £200,000 a year in severe patients (usually classified as SMA type 1 or weak type 2). As an example, a standard basic NHS care package for SMA type 1 that consists of a provision of a single night carer for 10 hour daily carries an associated cost to NHS of £109,500 (3,650 hours contracted at £30/h). Further disease-related costs for the taxpayer include, among others: planned hospital visits, unplanned hospitalisations (including at PICU/ICU – several times a year in SMA type 1), equipment (orthoses, ventilator, cough assist, specialised wheelchair, bed, standing frame, etc., all of which have to be regularly replaced as the child grows), house adaptations (LA packages of up to £50,000), school adaptations, additional school staff member (TA) or, sometimes, specialised schooling, physiotherapy, OT, cost of mobility / car adaptations, and finally, significant loss of earnings for the family (and the cost of associated disability/housing benefits and tax credits that usually have to be provided instead). While not all of the cost would disappear with treatment right away, based on RWE the majority of treated patients are expected to significantly improve functionally over time, with improvements expected to continue for the lifetime of the patient (due to the drug's mechanism of action). Furthermore, early initiation of treatment would in all likelihood prevent functional decline and, consequently, significantly reduce the need for highly specialised care packages. For instance, thanks to preventing respiratory deterioration – which nusinersen has been proven to do in the vast majority of treated patients – the treatment will make the £109,500 night care package unnecessary. Consequently, it is entirely plausible that in some subgroups of patients, the savings brought about by early pharmacological intervention may approach the drug procurement costs even at its list prices. It is worth pointing out that a HTA in even a relatively poor eastern European country Poland has assumed the annual medical and loss-of-productivity costs (excluding schooling, mobility and adaptations) in case of a SMA 1 type patient at approx. £95,000 (PLN 460,018). Summing up, TreatSMA is of the view that the disease burden has been severely underestimated in the company's economic model, whilst the Committee's expressed view that it has been overestimated is entirely unfounded.

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4	While we understand and share the global outrage at the list price of nusinersen, we need to stress that any pharmacoeconomic analyses that result in allowing or disallowing access to the only effective treatment should be based on the actual purchase price and the effective budget impact. We are aware that the manufacturer has offered substantial discounts and risk-sharing arrangements in other countries. We request that the nusinersen appraisal is reviewed in full accordance with the drug's label based on the manufacturer's full commercial offer.
5	NICE's continuous reliance on QALY analysis in determining the value of an intervention has been a subject of sustained criticism in academic circles, especially when it relates to interventions in orphan diseases. Currently, out of all EU countries, only UK and Poland use QALY as the principal determinant in reimbursement decisions, with Poland planning to move away from it at least in orphan diseases from 2019. All the other European countries use a QALY value as one of secondary parameters in HTA. Most recently, Scotland has established a separate appraisal pathway for orphan drugs in which the QALY analysis plays a supportive role. This is justified based on a distinct character of the majority of orphan conditions (80% of which are of genetic origin) as well as on different economic considerations related to the development of orphan drugs. We understand that it is not easy to change an established practice, but we, the SMA families, do not want to be hostages of a methodology that has long been discredited and replaced everywhere else with methodologies better suited to appraising orphan drugs. We need to underline that in all other European country, results of technology appraisal of nusinersen in SMA have been positive, which puts an even bigger question mark over the approach used by NICE to the detriment of thousands of those who suffer from SMA.

Insert extra rows as needed

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Comments

QUESTION: During the appraisal process the committee heard that nusinersen may have a relatively greater benefit for those with more severe types of SMA, but that the classification system does not always reflect the full extent of the disease. Boundaries between the different SMA classifications are blurred and can be subjective.

As part of your response to consultation we would welcome your comments on whether there is a clinically distinct subgroup of people in whom nusinersen is expected to be more clinically effective, and how this group could be identified in clinical practice.

In response to this question, we first need to note the distinction between *clinical effectiveness* and *practical benefit*. While clinical research attempts to quantify the former, patients are mostly concerned with the latter.

Defining a patient-relevant outcome

It is a challenge to properly define the practical benefit in SMA therapy. A 2015 survey of European patient and carer expectations from SMA therapies revealed that stabilisation of the disease progress alone is a significant and desirable outcome of treatment (Rouault, *et al*, 2017). As we know it, those with SMA and their carers experience a prevailing, continuous fear of a loss of a major motor milestone, as this type of deterioration suddenly (and likely permanently) increases the person's dependency on others.

Similarly, a clinically minor improvement may mean a disproportionately a lot to the patient in terms of *practical benefit*. For instance, a gained palm control (which is 1 point on HINE scale) opens to the patient the entire world of digital communication and enables environmental control through the gained ability to use touchscreen devices. A clinically minor change of gaining unsupported seating (again, a single point on the HFMS scale) translates, in terms of *practical benefit*, into the freedom of leaving home without carrying around a specialist toilet seat (which also means, a possibility to use other means of transport than car).

Predictors of treatment benefit

POOR PREDICTORS:

1. **SMA types**. The traditional classification into "types" is a fair predictor of survival but a poor predictor of the individual course and an even poorer predictor of treatment effect.

2. ***SMN2* copy number**. Even as the SMN2 copy number does not correlate well with the severity of symptoms or the disease course, nusinersen's mechanism may suggest that its clinical efficacy should correlate with the SMN2 copy number. This proposition has not found a convincing confirmation in clinical trials or post-MA use: Aragon-Gawinska, *et al*, has not found statistically significant difference in 6-month efficacy between SMA type 1 patients with 2 or 3 copies of the SMN2 gene.

3. **Age**. Due to the high variability of the disease course in individual patients, age alone is not a reliable indicator either of the amount of function lost or of the potential gains with treatment. Clinical data do not offer any cut-off age after which the treatment would become significantly less effective, and meaningful improvement was observed in clinical practice in patients of various ages, including in adults with type 1 SMA [redacted]

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PREDICTOR TO CONSIDER

Based on the disease and treatment mechanisms, nusinersen should have a stronger therapeutic effect in **patients in whom motor neuron damage and muscle tissue loss have not been significant.**

This will certainly include all presymptomatic patients. The NURTURE clinical trial has yielded interesting observations of nusinersen efficacy in presymptomatic (actually, mostly early symptomatic but fulfilling the study inclusion criteria) babies with presumed type 1 SMA. Some of those presymptomatically treated children are currently developing normally while others have various (but mostly minimal) delays in motor development.

We have observed similar normal development when nusinersen was administered to a 7-months-old early symptomatic girl who was to develop type 2 SMA, just like her elder brother. After 16 months of nusinersen treatment the girl is developing phenomenally, with no motor delays whatsoever ([redacted] video evidence from the family).

Similarly, even as controlled data is scarce, we can safely assume that initiation of nusinersen treatment in those who are still able to walk will likely allow them to remain ambulatory for the rest of their lives. This is corroborated by the encouraging 6MWT test results from the phase-2 trial.

If talking about urgency of treatment, then those at the start of disease course, when muscle function loss progresses fastest, should be offered treatment immediately, so as to minimise the damage caused by the disease. The time from first symptoms (but not necessarily from diagnosis) could be used for triaging.

Finally, we have been surprised to observe that adults show on average stronger effects than adolescents in a similar condition; this includes specifically adults with type 1 and weak type 2 SMA, in a few of them the effects have been spectacular! While this merits further investigation, we attribute this to more determination in carrying out daily exercise, which is absolutely crucial in muscle-wasting disorders.

The above is not to mean that the drug will not offer practical benefit in the majority of the SMA population as there is strong academic and patient-reported evidence, from all over the world, of **nusinersen efficacy across the entire spectrum of the disease.**

Insert extra rows as needed

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Nusinersen for treating spinal muscular atrophy [ID1069]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Paediatric Neurology association
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[redacted] has received compensation to participate in 1 scientific symposium organised by Biogen; and she has taken part in 1 Scientific Advisory boards organised by Biogen in which emerging data from Nusinersen were presented. [redacted] is part of SMA Reach and SMARTnet.
Name of commentator person completing form:	[redacted]

Comment number	Comments

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Nusinersen has clearly demonstrated a very robust therapeutic effect with highly significant positive results on the functional outcome of affected SMA children, their health and survival. Following studies in which the UK centres took part (Lancet 2016, PMID: 27939059; NEJM 2017 PMID: 29091570; NEJM 2018, PMID: 29443664) this drug was approved by FDA in December 2016, less than 4 months from the study end; and by EMA shortly after. Severely affected children with SMA1 (who never acquire sitting position and who typically die at a mean age of 9 months of life) now have the prospect of a therapy that – especially if initiated close to the onset of disease- can substantially reduce the complications we see in this disease, such as respiratory and feeding problems as well as improved motor skills such as sitting in some children and even standing. There is no doubt that Nusinersen is an effective therapeutic intervention for SMA, both from clinical experience as well as from the research publications. It is also clear however that delaying the initiation of treatment in this severe neurodegenerative disease leads to worse outcome. If initiated before 13 weeks of age, the results are very positive.
2	**Could Nusinersen be more effective in other SMA types?** For conditions like SMA type 3 with a less aggressive progression, a window of opportunity for improvement with treatment may be larger. In this condition approximately 80- 90% of children with SMA type 3, with onset before the age of three years (classified as SMA 3a), will lose the ability to walk by late teens. In a recently presented and publically available long term extension study of 14 children with SMA type 3 originally recruited in the Nusinersen clinical trial (NEJM), the Median (25th, 75th percentiles) distance walked increased over time by 17.0 (0.0, 51.0) meters at Day 253 and 98.0 (62.0, 135.0) meters at Day 1050. These figures therefore indicate a continued improvement on Nusinersen, as also mirrored in the SMA type 1 children.
3	**Nusinersen treatment for all SMA types?** We are aware, as clinicians, that children with SMA type 1 on Nusinersen are now becoming more able and stronger than our SMA type 2 children not on Nusinersen. This, to the parents, appears as discrimination. Whilst a clinical diagnosis, on whether a child can sit, stand walk denotes their SMA type clinically; 1,2,3 or 4, we are also aware that SMN2 copy numbers can also have a predictive value, and this was used in the clinical trials (SMN2 copy number =2). Whilst some SMA type 1 children generally have 2 copy numbers of SMN2, equally there are SMA type 2 children that also have this number and within the SMA type there is a clinical spectrum; SMA Type 2 can range from a weak type 2 (2.1) to a strong, almost SMA type 3 (2.9) child. Therefore to stipulate copy numbers of SMN2 is not feasible, however clinical judgement and response to a treatment should be taken into account. If a child is improving both motor milestones and respiratory but also time spent out of hospital, this is all beneficial and ultimately cost saving. If treatment with Nusinersen means that an SMA type 2 child behaves more like an SMA type 3 child, this reduces the medical costs and interventions significantly.
4	**High cost treatment; benefits?** We are fully aware that one of the concerns, explicitly expressed by NHSE and NICE relates to the perceived or likely high drug cost of Nusinersen. We completely understand that treatments should be cost effective and the lowest cost possible, weighing up the benefits and other costs incurred. Successful negotiations have been held already in 20 countries where Nusinersen is available to patients affected by early onset SMA (including Scotland), while the drug is anticipated to become available imminently in another 20 countries as a result of a clear path for approval. We support the robust processes to ensure appropriate drugs are funded, however the process on this occasion has been extremely lengthy and there has been no negotiation made with the company re; pricing.
5	The UK is number 1 in its ability to run effective trials and we have engaged with pharma companies to ensure that our children have access to these trials. However given the problems that are encountered by our processes to get drugs funded will have repercussions regarding Pharma's willingness to engage with the UK, in all drug related trials, and therefore this will have a detrimental effect to the degree of funding afforded to departments and the NHS, which will only serve to reduce our abilities to run 1st class clinical trials and be a world leader in this field.
6	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS**

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	Previously the standards of care adopted for care of these patients was purely supportive, however with the development and use of Nusinersen this has changed. The provisional recommendation of not considering Nusinersen would negate this and mean patients would be deprived the chance to gain motor skills rather than loose them and live rather than die. **We would not be in support of this.** In the UK we have collected data on all the children treated with Nusinersen to date and up until now we have not had any deaths, no adverse events and all children have continued to improve or stabilise. This data has been discussed and presented at a national workshop where paediatricians, paediatric neurologists, respiratory physicians and physiotherapists, and intensivists from the entire UK attended. We as clinicians are collecting data and entering this as part of a national database monitoring closely the effectiveness in real-time of these children on the Nusinersen as part of the EAP.

Insert extra rows as needed

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Nusinersen for treating spinal muscular atrophy [ID1069]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[redacted]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[redacted] is a principal investigator in the Biogen sponsored SHINE study (infants with type I SMA). In addition [redacted] has received compensation to participate in 2 scientific symposia organised by Biogen; and he has taken part in 2 Scientific Advisory boards organised by Biogen in which emerging data from Nusinersen were presented. Finally Great Ormond Street Children's Hospital where [redacted] works has received a grant ([redacted]) to set up a SMA registry that could be used to capture the SMA disease course
Name of commentator person completing form:	[redacted]

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1	**Has all the relevant evidence being considered?** In our view the relevant evidence has not been sufficiently considered: When referring to the reported literature, there is no acknowledgement of the fact that in the relevant clinical trials as well as in the already ongoing Extended Access Program (EAP), nusinersen is given to children with already well-established disease rather than to those still at an earlier disease stage. This is an important point, as infants with shorter disease duration had a considerably better response both from a motor and (in the case of SMA type 1) respiratory perspective, as has been well-documented in two seminal papers in the New England Journal of Medicine (Mercuri et a, N Engl J Med. 2018 Feb 15;378(7):625-635; Finkel et al . N Engl J Med. 2017 Nov 2;377(18):1723-1732) reporting the outcome of the relevant clinical trials. This observation is not unexpected, as at the advanced stages of the disease motor neuron loss has already accelerated. It is, on the contrary, almost surprising that children recruited at a more advanced disease stage through the EAP in most instances show some - although limited - motor response. If nusinersen was adopted, and became the established standard of care, it would be administered as soon as possible after the diagnosis, and the results would therefore be at least comparable to those reported in the NEJM papers reporting the outcome in children with shorter disease duration. We feel that it is therefore of utmost importance that when the outcome of the relevant studies is assessed, the timing of the intervention is considered in the context of the biology of the underlying motor neuron disease. The only modest improvement observed in children affected by type 1 SMA who start to receive the drug only at a more advanced disease stage is not unexpected, as it would not be unexpected that, for example, an in principle effective antineoplastic therapy will only achieve a modest effect if administered to individuals with already advanced metastatic cancer. It is almost surprising to see that even after a long disease duration, a substantial proportion of SMA patients can still demonstrate motor improvement after nusinersen, as reported by multiple groups reporting the real world evidence from the EAPs worldwide. Clearly the extent of response even in this very advanced population is more variable compared to early symptomatic children, and we urge the committee to apply both the knowledge on the biology of the disease and assessment of all published evidence including timing of drug administration and clinical response. A number of recent papers that provide real life experience of the drug and stress the overall positive experience found by these investigators is reported below Aragon-Gawinska, K et al (2018) A cohort study Neurology® 2018;00:1-7. doi:10.1212/WNL.0000000000006281 Farrar, M et al (2018);89:937–942. doi:10.1136/jnnp-2017-317412 Pechmann, A et al (2018) Journal of Neuromuscular Diseases 5 (2018) 135-143 DOI 10.3233/JND-180315 Pane, M et al (2018) Neuromuscular Disorders 28 (2018) 582-585 30 May 2018 Mousa, M et al (2018) # Springer-Verlag GmbH Germany, Springer Nature July 2018 Veerapandiyan, A et al (2018) Neurology® 2018;91:e620-e624

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2	**Concerns regarding the long term effect of the drug**. While the committee reiterated multiple times that there are concerns regarding the long-term effect of the drug, there is never acknowledgement of the fact that treated patients in each of the published studies continue to show improvement, and do not appear to peak in their abilities, let alone demonstrate deterioration. The fact that children with more advanced disease and in particular those recruited in a real world setting through the EAP may not experience improvement or may in some instances deteriorate is not unexpected, taking into account the biology of the disease with already accelerated motor neurone loss at this stage. However, as outlined above, this observation cannot be considered an argument for withholding treatment from infants at an earlier disease stage, who have demonstrated robust and sustained improvement in the relevant clinical studies. We need to keep in mind that any drug acting by promoting SMN production will have maximal efficacy in the next generation of patients, as these will be the patients in whom better outcome is expected based on all the available literature and experience. The data supporting this argument are clearly presented in the 2 publications reporting the outcome of the original nusinersen studies (Mercuri et a, N Engl J Med. 2018 Feb 15;378(7):625-635; Finkel et al . N Engl J Med. 2017 Nov 2;377(18):1723-1732.. This lack of acknowledgement by the committee of a slow but continuous improvement in the majority of treated children, while stressing the possibility of long term deterioration, is a concern to us as it does not capture the peer reviewed published evidence.
3	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** In our opinion the answer to this question has to be “No”. While Biogen, the manufacturing company, may perhaps have provided an overly optimistic assessment of the possible benefits, in our opinion the committee provided a far too pessimistic evaluation. In particular, this evaluation does not at all take into account the experience in children receiving the drug relatively early in the disease, the group of patients which will represent the majority of the treated patients after the current patient population has been treated. If one takes this into account, it could well be that the evaluation from the company represents a closer adherence to reality compared to the view of the committee. Furthermore, we note that the QUALY measurement is not a suitable tool for the evaluation of rare and devastating diseases such as SMA type 1 and 2 using, also reflected in the fact that the QUALY measurement has not been used as a tool in other similarly rare and devastating conditions. The individual and societal disease burden that conditions like SMA1 and 2 (and to a lesser extent the later-onset types 3 and 4) carry for is currently not well-captured and generally underappreciated by those not directly affected by these devastating and profoundly disabling conditions. We are also concerned that NHSE and NICE do not have accurate figures on which to take the decision of not having SMA being evaluated via the highly specialised route, which would clearly represent an appropriate route for the evaluation of this type of intervention. The committee appears to recognise that SMA is a rare and devastating condition; to however recommend the blunt QUALY tool for its evaluation, a tool fit for the purpose of common and less complex conditions
4	**Are the provisional recommendations sound and a suitable basis for guidance**

	to the NHS? The provisional recommendation are not a suitable basis for guidance to the NHS, as by not considering nusinersen treatment, patients with SMA will be deprived of the perspective of improved motor function and prolonged. We do therefore not support these recommendations. We also note that despite the advanced disease stage at the point of recruitment, the fatality in the SMA1 population recruited under the EAP commenced in the UK in August 2017 has dramatically decreased. We have indicated above that motor function improved in the majority of these patients despite the already advanced stage of disease at the time nusinersen treatment was commenced. We can also report that in some of the children who have been recruited more recently following a shorter disease duration, a reduction of respiratory requirements could be observed. These data were discussed and presented at a national workshop organized by our group, involving paediatricians, paediatric neurologists, respiratory physicians and physiotherapists, and intensivists from the entire UK We also note that the commercial availability of Nusinersen for SMA 1 in Scotland brings equality challenges that families and physicians will be forced to face given the current NICE recommendations. Given the announced decision from Biogen to terminate in November 2018 the EAP for SMA1 after 2 years from its inception, this will represent discrimination against families living in England and Wales
5	**Are the boundaries between different subtype of SMA clear or blurred**. We do not agree that the boundaries are blurred, as SMA subtypes are diagnosed according to clear clinical criteria, recognised for centuries and the maximal functional abilities that inform these clinical criteria are typically reached at the time of the diagnosis in the overwhelming majority of patients. For example, at the time of diagnosis, essentially all patients with type II SMA would have already acquired the ability to sit (an exclusion criteria for SMA1) and patients with type III SMA would have acquired the ability to walk (an exclusion criteria for SMA1). It is correct that in exceptional cases there can be some patients who are on the clinical boundary of two different subtypes (for example a child, “almost able to sit”), however, these cases are rare, and an expert clinician should be able to recognise these rare exceptions.
6	**Requested comments on whether there is a clinically distinct subgroup of people in whom nusinersen is expected to have better efficacy.** As indicated before, the published literature suggests that SMA type I children with a shorter disease course clearly benefitted more than children with longer disease duration (Finkel et al, NEJM2017); comparable findings have been documented in children with type 2 SMA (Mercuri et al, NEJM 2018). For conditions like type 3 SMA the less aggressive progression most likely indicates that the window of opportunity for improvement is even wider. Of note, between 80-90% of children with type 3 SMA with onset before the age of three years (classified as SMA 3a) will lose their ability to walk by their late teens, emphasizing the need for therapeutic intervention also in this group. In a recently presented and already publically available long term extension study of 14 children with type 3 SMA originally recruited in the nusinersen clinical trial, the median (25th, 75th percentiles) distance walked increased over time by 17.0 (0.0, 51.0) meters at Day 253 , and by 98.0 (62.0, 135.0) meters at Day 1050 (Montes et al, 2018, Cure SMA meeting proceedings). These figures contrast with all published literature on the natural history of children with SMA3 and demonstrate that the nusinersen effect, if anything, builds up over time

Nusinersen for treating spinal muscular atrophy [ID1069]

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Dear Helen

The scientific data for efficacy of nusinersen, is recent. My recommendation is below are based on the scientific data and deduction from first principles of management of SMA, and the underlying pathogenesis.

My suggested priorities in terms of need and effectiveness are listed below:

1. spinal muscular atrophy type I, especially new onset cases

2. spinal muscular atrophy type II - under 3 years of age

3. spinal must atrophy type IIIA (onset of symptoms under 3 years of age) . When they are in the first 3 years of life (or 4 below)

4. SMA type III , with worsening of motor function and risk of loss of walking

5. SMA1 and 2 infants, in the presymptomatic phase, diagnosed on the base of genetic testing, in families where there was a previous history of spinal muscular atrophy. In practice, this would mean offering the treatment to SMA infant's with SMN2 copy number of 4 or below

Category five, though listed at the end and anticipated to have small numbers, is a priority, as it is likely to prevent or significantly significant ameliorate disease symptoms which would develop later in future

Best wishes

Adnan Manzur

Nusinersen for treating spinal muscular atrophy [ID1069]

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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:	Elizabeth Lockley

Comment number	**Comments**

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Example 1	We are concerned that this recommendation may imply that ……..
1	I am concerned that there are lots of children (including my type 2 son) who are receiving NO treatment. They have NO other option. As a consequence, these **children are getting weaker as they grow**. **This increased weakness is going to create more health, physical, emotional, medical and care needs** which in turn will increase already under estimated care costs. Type 2 children are already expected to be able lead long lives with fulfilling careers. With treatment these children could achieve this more independently, have less care needs and avoid major medical interventions. For example, if a patient had enough arm strength to self-transfer on / off a toilet this would avoid the need for hoisting systems and carers. Or if they had enough muscle strength to support their spine as they grow, then invasive spinal surgery and increased hospitalised for chest infections could be avoided.
2	**I feel that the cost effectiveness of this drug has been hugely underestimated.** A lot of the care needs and medical and equipment costs are swallowed by the patient's family, including the potential sacrifice of careers. Also, the smallest gains in strength, which may seem insignificant, could dramatically change a life and increase independence. (E.g. the strength to operate a joystick on wheelchair or a tablet.)
3	**Sub groups** I agree that types are NOT an accurate way of grouping patients. Boundaries are blurred between types and can be subjective. Also, now some Type 1s on the Early Access Programme are becoming stronger and are now achieving milestones which would clinically class them as Type 2s. Evidence suggests the sooner the patient is given the drug the more benefit it could give. However, I do not feel that anyone should be denied a drug that could benefit then. It will be extremely difficult to draw the line anywhere. I am aware that during periods of rapid growth (e.g. puberty) patient's decline can be exacerbated and they can weaken further. Therefore, it would be good to have treatment pre-puberty to avoid this. However, different children go through puberty at different times and denying post puberty patients the drug could also add to teenage angst and create further problems. I feel the only initial option is to offer to ALL types and ALL ages for at least a determined trial period.
4	
5	
6	

Insert extra rows as needed

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Name	[redacted]
Organisation	
Role	Carer
Job title	Parent of sma type 2 child
Location	England
Conflict	No
Disclosure	
Comments	This drug is so important to all the parents who care for sma children it's not fair for them to live like this when there's a drug out there that can improve there life it shouldn't even be a question to not having it we should ! Despite the money it costs improving a sma child's life & health outweighs anything

Name	[redacted]
Organisation	
Role	Carer
Job title	Leisure Supervisor
Location	England
Conflict	No
Disclosure	
Comments	You state that there are is no long term evidence for this treatment, however, the trials lasted 5 years and the drug was fast tracked by the FDA because of the benefits it showed during the trials, and was also fast tracked by the EMA in May 2017. I don't know how long the panel thinks trials should last when they have shown significant benefit to a population of patients who do not have any other treament approved for SMA You state that there is an unmet need for effective treatments that could slow progression, but by denying this treatment which is an effective treatment you are not meeting the needs of the patients You stated you considered a wide range of factors while appraising Nusinersen, one of which was for end of life treatments. This is a facor which is considered for cancer patients and has no bearing for the treatment and consideration of a treatment for a RARE condition You say that Nusinersen cannot be recommended due to cost effectiveness, but you do not state what would be an effective cost? Surely there must be a threshold where you would consider it to be cost effective, and this has to be discussed between NHS and Biogen You mention that you also considered a proposed commercial arrangement. What was this arrangement, and if this was not suitable, surely this was the time to discuss one that would suit? You state that people with type 2 are often severely disabled and unable to walk unaided. The truth is that type 2 patients are

	unable to walk at all. Maybe the committee should have the proper data before they appraise? Patient experts described the blurring between the types often leading to a misunderstanding of the condition. Clinical experts accepted this but decided that the current classification system is the most accurate predictor. How can you say this when patient experts who deal with many SMA patients every year have a better understanding of the condition than you do? The committee acknowledged that Nusinersen should be considered for all types as per it's marketing label, but then commented that Biogen had no data for types 0 and 4. When they looked at the data surely they would know that the trials were only taken place for certain types and therefore in my opinion you are picking at any little thing that may make this medication look bad, and in my opinion this is disgraceful. It clearly states that 51% of patients in the ENDEAR trial reached motor milestones compared to 0% in the sham group. In fact this trial was stopped early and all children put on Nusinersen because it was unethical to keep them on a sham treatment when the actual drug was so effective. Surely this indicates that this treatment is effective Again the committee doubts the long term effectiveness of this treatment. So is it ethical to just not recommend it and withdraw it from a population who need an unmet need for some kind of treatment. Surely it would be better for patients to try it than to not have access at all? The committee said it was plausible that SMA left untreated would worsen but implausible that SMA treated with Nusinersen could not get worse, as some patients treated with the drug still got worse. Surely this indicates that the treatment may affect on an individual basis so therefore every patient should have the right to at least try it and possibly put stop criteria in place if the patient has 2 appointments where there is no improvement in any of the scales. so you could say 2 years or 9 injections, if no improvement then the treatment is stopped? The committee also heard that the population eligible for Nusinersen includes people with disabilities. Really? I thought that this would be obvious and wouldn't have to be stated. So could we argue that based on people being disabled, you have refused the treatment on these grounds, so therefore it is discrimination? The committee stated that Nusinersen met the end of life criteria for early onset SMA but not for the later onset. I think it should be pointed out that it is not all about extending life. Nusinersen has been proven time and time again to improve the motor and respiratory function of SMA patients. Although you keep stating there is no evidence that it prolongs life, surely the fact that patients improve in other ways and can in fact have

	their life improved by any slight motor function improvements, which will then open up a whole new life by being able to access touch screens, powered wheelchairs and being able to move a finger or hand to enable them to communicate with others through different media sources is better than not giving them the treatments at all.

Name	[redacted]
Organisation	Not commenting of behalf of an organisation
Role	PublicNot commenting of behalf of an organisation
Job title	n/a
Location	England
Conflict	No
Disclosure	
Comments	A complete travesty of a decision for anyone suffering from SMA and their friends and family. If this outcome is financially driven, then I'm even more disgusted given the fact that this treatment has proven results for a condition that currently has no alternative. Please consider that time is crucial for those with SMA and find a way of resolving this quickly, with compassion for those that this decision affects.

Name	[redacted]
Organisation	
Role	NHS Professional
Job title	GP (retired)
Location	England
Conflict	No
Disclosure	retired GP - occasionally working as a locum
Comments	Although I appreciate the comments in relation to a population of SMA sufferers, you cannot get away from the life-changing benefits to some. It must be possible to trial this for all sufferers and then look at who benefits. Even arresting this disease is a benefit, improving it is a miracle. We routinely spend this sort of money on other treatments and regimes.

Name	[redacted]
Organisation	
Role	NHS Professional
Job title	Consultant Paediatric neurologist
Location	England
Conflict	Yes
Disclosure	I am a clinican who provides care for babies with SMA - this includes provision of nusinersen via an expanded access programme supported by Biogen but which wil now be closed to any new cases. I have undertaken advisory work for Biogen.
Comments	The outcome of the NICE appraisal process is very disappointing. Other European countries have accepted the evidence provided that supports the benefits of nusinersen treatment for SMA in terms of promoting quality of life and preventing/ delaying respiratory failure. This is a lethal condition for which there is no other treatment, any child now born with this condition in England will develop respiratory failure and either require long term ventilation or die in early infancy. An urgent re-appraisal is therefore necessary to determine how those born with this devastating condition can access treatment within the NHS. The treatment is most likely to be beneficial if staretd within the earliest stages of symptoms and therefore any delay in providing treatment disadvantages those with this devsatating condition. It seems to me to be entirely unethical not to be providing this potentially life transforming treatment.

Name	[redacted]
Organisation	
Role	NHS Professional
Job title	Senior paediatric physiotherapist
Location	England
Conflict	No
Disclosure	no
Comments	As a community physiotherapist I have had the experience in being part of a families devastating journey with a baby who died of Type 1 SMA before Nusinersen was available and am now involved with a family who are undergoing an entirely different experience with a type 1 baby who is receiving Nusinersen. Her progress has been remarkable she has gone from a floppy baby unable to interact due to no head control or active movement of limbs to a child that can sit independently after 12 months of treatment. She is able to play, feed herself, drive a motorized wheelchair and is a delight to all around her. She is thoroughly enjoying life and it is Nusinersen that has made the difference. There is no alternative treatment available and I am devastated to think that the next baby with SMA that is referred to me will not have this chance. I cannot imagine how I will be able to explain to parents that the NHS of which I am a proud member has made such a decision based on finance alone. I implore you to work with Biogen to reach a financial agreement so that this treatment can be offered to all.

Name	[redacted]
Organisation	
Role	Carer
Job title	
Location	England
Conflict	No
Disclosure	
Comments	Our son, [redacted], is two years and 10 months old and has SMA type 2. [redacted] SMA has had a massive impact on all of our lives; from the age of 12 months when he began to become reluctant to stand, after previously loving exploring our house as he crawled around, through the early days of diagnosis aged around 16 months, up until the present day. SMA will progressively affect every single muscle in his body. Right now [redacted] can sit and play, but his muscles have slowly lost the strength to help him stand, crawl or walk. He can lift his hands to raise a spoon or cup to eat and drink, but is beginning to find it difficult to raise his head should it flop onto his chest. He cannot roll or move in bed when he sleeps. He needs daily medicine to help him with chronic constipation. He also uses a cough assist machine each morning to help clear his lungs as his breathing is compromised by his condition as he cannot fill his lungs adequately. He is completely dependent on us, his parents, for every aspect of his care. Yet perhaps the worst part of his condition is the knowledge that as he grows, each and every day he will get weaker. His current situation will only worsen. He will not gain skills or new abilities like other children. Photographs will not show him growing stronger, they will show what he used to be like, and that he was stronger in these photos than today and we know that tomorrow he will be weaker. This knowledge is an awful emotional burden for us all, [redacted], his parents and wider family, to bear. We are watching our son slowly slip away from us; can you imagine anything crueller? Because we have a positive attitude to SMA we will not give up. We just get on with our lives as best we can, but sometimes it's important to reflect on the extra challenges we face. Since November of 2017 we have endured 6 emergency hospitalisations for chest infections. We have managed just as many infections at home. Each time [redacted] has to undergo a variety of painful and stressful procedures, such as nasal and oral suction, tube feeding and rigorous physiotherapy. We have multiple appointments with a myriad of medical professionals: orthopaedics, orthotics, respiratory, occupational therapy, dieticians and neuromuscular departments to name just a few. As his lumbar muscles weaken he is developing a scoliosis and uses a variety of supportive orthopaedic seats. Our house is full of equipment, like standing frames, supportive play chairs, adapted baths as well as a motorised wheelchair. We will be adapting our home to improve access for his wheelchair, as well as modifying the garden to give him the opportunity to explore the space independently. We are now awaiting a BiPAP assisted-breathing machine, which will require [redacted] to wear

	a mask but will help him fill his lungs more effectively, adding to the list of interventions this beautiful 3 year-old boy has to face on a daily basis. Finally, all trips and excursions are meticulously planned; will he need his cough assist? What medicines will he need? How will he sit? What chairs do we need? What toilet facilities are there? [redacted] is an incredibly bright, articulate and intelligent child; he is constantly amazing us with his insight and memory for detail. He is becoming more self-aware, and he is learning that he is different and he cannot play with his friends like he wants to. He loves going to nursery three days a week and has many friends who love him and miss him when he is sick, which unfortunately has been far too often. He has the right to an education like every child, and is learning so much, so quickly. We all believe, family, medical team and teachers, that [redacted] has a bright future, but that all depends on how we can battle this punishing condition. We know that without treatment, [redacted] will become progressively weaker as he grows up. We know that his life will become harder, and in all likelihood, shorter. His breathing will become more laboured, his swallow less strong. He might need a colostomy bag. He might need breathing support 24 hours a day. His quality of life will worsen steadily. Nursinersen gives us all hope for a better future. From our SMA friends at home and around the world, we know the impact that the drug can have and, while we know that its effects are still being understood, we are desperate to give [redacted] the chance he deserves. [redacted] looks like so many of the type 2 children we see in America, in Europe or Australia, with their familiar thin arms and legs and folded bodies, yet still they beam, with beautiful sunny smiles. And to see those children, with type 2, improving, pushing to stand, to walk, to cough more strongly or to raise their heads, as the Nursinersen strengthens them is a miracle. Yet it is a miracle we, in this country, are being denied. We want the opportunity to try Nursinersen, and as [redacted] parents we will do everything in our power to make it happen. We strongly urge NICE to reconsider their decision, for the sake of our son, and for every person and family in the UK suffering with SMA.

Name	[redacted]
Organisation	
Role	Carer
Job title	
Location	England
Conflict	No
Disclosure	
Comments	My Granddaughter has SMA type 2 - she will be 3 years old in November. Since diagnosis in January 2017, we have seen the SMA Community campaign tirelessly for access to SPINRAZA for all those who would benefit. The consultation paper is

	obviously disappointing in that NICE are not recommending SPINRAZA for funding by the NHS at this stage. We note however that NICE's consultation paper encourages the possibility of a Managed Access Agreement and that talks are taking place with NHS England and Biogen. There is no doubt that the current price of SPINRAZA is expensive but surely it should be weighed against the cost of hospital visits, medication, machinery and the involvement of a multi-disciplinary team for someone who does not receive SPINRAZA. It is obvious but disappointing that SPINRAZA is too expensive to be assessed under the Single Technology Appraisal route. However, it should also be considered that apart from the first year of treatment, the current price of Â£225,000 falls below the HST limit. It would therefore seem that there must surely be some room for negotiation. At nearly 3 years old, My granddaughter is now old enough and bright enough to realise that she is different to other children. My Granddaughter attends full time Nursery and never gives up trying to be independent but her frustration and sadness at not being able to walk and do as others do, is increasingly evident. Of course, we have no answers for her. It should also be borne in mind that SMA does not just affect the patient. Her parents struggle every day with an unpredictable and often hopeless situation, in the face of which they still strive to provide her with the best quality of life that they can. As many parents do, they both work full time and have to manage this around hospital admissions and appointments with various experts within a multi-disciplinary team on an ongoing basis. This is both time consuming and at times, soul destroying. For us as Grandparents, it's an incredibly difficult and impossible scenario. As much support as we try to provide, our son and daughter in law are devastated and we see our Granddaughter struggle every day. The long term psychological and physical effect on both her parents, the family and us are quite apparent. Since her diagnosis in January 2017, good quality sleep and rest are bygone and impossible luxuries. We are consumed with trying to make things better, but for us and other families like ours, there desperately needs to be a light at the end of the tunnel. We are all well aware that SPINRAZA will not cure SMA, but as parents and Grandparents, we want to know that our granddaughter and all children like her, are given the best possible chance of quality of life and survival that it is possible to give. For these reasons, we would ask that NICE reconsider their position to do everything possible to allow SPINRAZA to become available as soon as possible for SMA of all types.

Name	[redacted]
Organisation	
Role	Loving parent of an under 18 with SMA
Job title	
Location	England
Conflict	No
Disclosure	
Comments	I am writing to you regarding access to the spinal muscular atrophy (SMA) treatment called Spinraza for those under 18 years of age in the UK. Spinraza is the first and only treatment for patients with the rare inherited muscle-wasting condition spinal muscular atrophy (SMA). There are up to 1,300 children and adults living with SMA in the UK. For those who do have the condition, such as my three year old daughter, life without this treatment leads to muscle degeneration resulting is the loss of ability to walk, swallow and breath. There are also significant social, emotional, and financial implications for caregivers such as my wife and I. Spinraza has been licenses across Europe, including the U.K., since June 2017. Children in other countries where the drug is funded, such as Australia, America, the Nordics, and much of Europe, have shown life changing improvements and in many cases the ability to live a normal and productive life. In essence the lack of funding makes the U.K. seem a third world country when it comes to the provision of new medicines. This is increasingly strange when the government is advertising that it is putting billions of pounds of additional money into the NHS. Even Greece and Portugal, both of which have much lower per-capita incomes than Britain, completely subsidize Spinraza for patients. The NICE evaluation says that the drug provided a substantial clinical benefit. When I see the benefit those with Type 2 SMA have gained, including the ability to walk and run, in U.S. after being treated with Spinraza, I believe the NICE assessment to be a gross under estimation. This is a devastating disease which forces family and caregivers to watch the slow degeneration of a child to the point they can no longer move and die. Please could we ask you to reconsider the NICE recommendation to include all children under 18 years of age.

Name	[redacted]
Organisation	
Role	Carer
Job title	MANAGING DIRECTOR
Location	
Conflict	No
Disclosure	

Comments	My Granddaughter has SMA type 2 - she will be 3 years old in November. Since diagnosis in January 2017, we have seen the SMA Community campaign tirelessly for access to SPINRAZA for all those who would benefit. The consultation paper is obviously disappointing in that NICE are not recommending SPINRAZA for funding by the NHS at this stage. We note however that NICE's consultation paper encourages the possibility of a Managed Access Agreement and that talks are taking place with NHS England and Biogen. There is no doubt that the current price of SPINRAZA is expensive but surely it should be weighed against the cost of hospital visits, medication, machinery and the involvement of a multi-disciplinary team for someone who does not receive SPINRAZA, as well as lost days at work for parents and the cost of stress and anxiety. Not everything can be measured in terms of money. It is obvious but disappointing that SPINRAZA is too expensive to be assessed under the Single Technology Appraisal route. However, it should also be considered that apart from the first year of treatment, the current price of £225,000 falls below the HST limit. It would therefore seem that there must surely be some room for negotiation. In addition, when my Granddaugher was diagnosed, we were told that her life expectancy was "early teenage years. Therefore the evidence that is so far available surely suggests that this is a life saving treatment. At nearly 3 years old, My granddaughter is now old enough and bright enough to realise that she is different to other children. She attends full time Nursery and never gives up trying to be independent but her frustration and sadness at not being able to walk and do as others do, is increasingly evident. And of course, we have no answers for her. It should also be borne in mind that SMA does not just affect the patient. My son and daughter in law struggle every day with an unpredictable and often hopeless situation, in the face of which they still strive to provide their daughter with the best quality of life that they can. As many parents do, they both work full time and have to manage this around hospital admissions and appointments with various experts within a multi-disciplinary team on an ongoing basis. This is both time consuming and at times, soul destroying. For us as Grandparents, it's an incredibly difficult, if not impossible scenario. As much support as we try to provide, our son and daughter in law are devastated and we see our Granddaughter struggle every day. My daughter in law needs to take anxiety medication and has counselling. The long term psychological and physical effect on both parents, the family and us are quite apparent. Since [redacted] diagnosis in January 2017, good quality sleep and rest are bygone and impossible luxuries. We are consumed with trying to make things better, but for us and other families like ours, there desperately needs to be a light at the end of the tunnel.

	We are all well aware that SPINRAZA will not cure SMA, but as parents and Grandparents, we want to know that all children with SMA, are given the best possible chance of quality of life and survival that it is possible to give. For these reasons, we would ask that NICE reconsider their position to do everything possible to allow SPINRAZA to become available as soon as possible for SMA of all types.

Name	[redacted]
Organisation	
Role	Carer
Job title	
Location	England
Conflict	No
Disclosure	
Comments	My son is 16 years of age and has SMA 2. The impact on our lives is devastating. [redacted] relies on me and his dad for all his personal care. He requires moving in bed at night frequently(at least once an hour) which has a knock on effect on our days, tempers and energy. As a result we both could no longer work so his dad is now at home full time, decision based on income rather than personal desire. We have at least 1 appointment a week either to a hospital or a health visitor to the home. Last year he couldn't do a full week at school because of ill health and appointments so one of us needs to be full time carer. Then we moved house because our last house couldn't be adapted for [redacted], this move came at a huge financial cost to us. Holidays as a family are expensive because of all the additional equipment plus adapted accommodation isnt easy to come by for a family so we book way in advance and 2 out of 3 times have been cancelled last minute as he becomes unwell. His brothers put up with a lot because of SMA as they miss out . [redacted] social group is nil since turning 15/16 as the gap between his abilities and his friends became too large to bridge. Parties, getting on a train to head into town, hanging out at a friends needs planning and an adult, actually any trip involves a lot of planning and cost. [redacted] feels the cold more especially his hands, so we have handwarmers and heating on. He doesn't like getting dressed or undressed unless the room temperature is tropical. He has me and his dad plus his brothers as main carers. We cant go out as a family now because he needs to be close to equipment should he suddenly have chest problems to date his dad and I haven't been out together in 6 years alone. The impact SMA will have without treatment is a continued downward trajectory. [redacted] lost his swallow this year and we can see he is now having difficulty keeping his head up. His cough is not as strong as it was 12 months ago. He has all the emotions of a teenager, doesn't believe he has a place in this world and I have to be hard on him to get him to believe he has a future. Though in my heart I am not sure how long his health will hold out. Knowing there is a treatment and not having access was like having [redacted] diagnosed again and so hard to accept, too hard to accept. My son is bright, funny and handsome I see his old friends who have half of his personality moving on with their lives and my wonderful son who has put up with so much is having his body turn into a prison. Its unbearable some days.

Name	[redacted]
Organisation	
Role	Concerned member of the public
Job title	
Location	England
Conflict	No
Disclosure	
Comments	Spinraza has been shown to have significant benefit in those countries that have adopted and funded it and as usual the UK is lagging behind with a negative, indecisive outlook. It is at present the only treatment available (subject to funding) and does benefit recipients. Fund it!

Name	[redacted]
Organisation	
Role	Public
Job title	Grandmother, Mother, Wife
Location	England
Conflict	No
Disclosure	
Comments	Why oh why is the UK dragging its heels yet again. How many children/families will have to suffer whilst the powers that be procrastinate. This treatment will enable all involved to have better lives. What will be the cost of the 24 hour care in all aspects of everyday life that is waiting for children with this terrible condition?

Name	[redacted]
Organisation	
Role	Carer
Job title	None
Location	
Conflict	No
Disclosure	
Comments	Clearly there is no long term evidence as nusinersen is a new treatment for a chronic disease. I understand there is now data (albeit outside the RCT setting) out to 5 years from the first recruited trial participants. Was this discussed? If not, why not? It would be limited but informative on longer term effects. I cannot emphasize this enough, sma is a devastating diagnosis that destroys the quality of life of an entire family My child has SMA 2/3 and was symptomatic at 18 months. She has now received 5 doses of nusinersen. We sought treatment in the USA and felt we had no choice but to leave our home and family. It was that or watch our beautiful daughter fade away. A negative opinion by NICE would mean that we would be unable to return to the UK and, when we are ultimately obliged to, we will have to watch her slowly loose the strength and function she has gained and explain to her why she can no longer have her 'magic medicine'. Lack of treatment would mean additional appointments to supervise her decline, increased respiratory issues, difficulties attending mainstream schooling, little social opportunities with friends (her or us) and the need for an adapted home when the time comes for a wheelchair. Ultimately she would need ongoing care and an adapted home as an adult. I would not be able to maintain my current employment even part-time with these additional demands and would become a full-time carer on a permanent basis. Receiving an SMA diagnosis for your child is utterly devastating. All the hopes and dreams you hold for your child are replaced by the certain knowledge that they will loose their strength and independence. The measureable and sustained improvements we have witnessed after only 5 doses have given

	us hope and we are confident that as long as we can access treatment her future is once again bright and shiny. Here is the US, nusinersen is the norm, SMA is no longer a devastating diagnosis. Once the roll-out of newborn screening is complete then SMA will effectively cease to exist as newborns will be treated at birth never developing symptoms. I have worked in HTA for over 15 years now and for the UK to falling so far very behind the US, europe and Australia the system is clearly not fit for this purpose.

Name	[redacted]
Organisation	
Role	Carer
Job title	
Location	England
Conflict	No
Disclosure	
Comments	As the mother of a 33 months old with Type 2 SMA, I am heartbroken by NICE's recommendation. I understand that Biogen's price tag for the drug is exorbitant, and I understand that the NHS has funding concerns, but how much is a child's life/quality of life worth? When the NHS is wasting lots of money in bad management and administration (which I have personally witnessed - alongside some very good people doing a fantastic job), when the NHS/NICE pays for the treatment of conditions which are self inflicted and is considering covering the cost of e-cigarettes, when they will pay for IVF treatment for babies to be produced against what mother nature would do, where is the fair use of funds in that. I could explain again the impact of this condition on my daughter but I have already submitted evidence to NICE for the first stage of the consultation and I know that Treat SMA and the SMA charities made it very clear to NICE already, so I have lost the energy to repeat it again. My heart is broken knowing that there is a medication available that would very likely enable my daughter to walk (words of the leading SMA specialist in France), that would slow down the progression of this horrible condition, that would allow her to not rely on me or someone else to wipe her bottom for the rest of her life, to take her to ICU when she gets severe chest infections, to pick toys up when she drops them, but no, I cannot give it to her. I hold the drug company most in contempt for the price tag they have put on it, but also feel ashamed by the choices of what is and what isn't provided by our national healthcare system.

Name	[redacted]
Organisation	
Role	Relative
Job title	Retired
Location	England
Conflict	No
Disclosure	The assessment model which NICE has used to reach the conclusions and make the recommendations outline in the consultation document is almost completely negative and mainly concentrated on a flawed analysis of cost-effectiveness. NICE should change this m
Comments	I am aware of children with type 2/3 SMA who have been receiving treatment with Spinraza for 18 months in the USA. Their life experience and ability to function physically have been transformed by this treatment. Intellectual assessment have placed some children at the 96th percentile and they regularly exceed educational expectations. Without Spinraza they would be unable to access school and would probably no longer be

	with us. Having read the NICE consultation document I find it very worrying that NICE does not acknowledge the research that led to Spinraza being provided for children with ALL forms of SMA across the globe. Cost effectiveness seems to be NICE's main concern. If countries like Greece with all of its financial problems can find the money to fund Spinraza for all SMA diagnosed children, then I believe the UK has a moral duty to follow suit. Other countries such as Australia, Spain and the USA (and many more) have accepted the transformative effect that Spinraza has had on children with all forms of SMA and their families. I am at a loss to understand why NICE should interpret research data in such a negative way when so many other countries are being so positive about the effects of Spinraza. Families want to live and work (and go to school) in their home country of the UK (specifically England). I urge NICE to reconsider the recommendations in its consultation document and to recommend that Spinraza should be made available on the NHS for children with ALL forms of SMA.

Name	[redacted]
Organisation	
Role	NHS Professional
Job title	Consultant paediatric Neurologist
Location	England
Conflict	No
Disclosure	PI for sideros study in DMD
Comments	In an ideal world with all the available resources it would be wonderful to have the treatment with Nusinersen available for all children with SMA except type 0. Short of that, in my experience the ones with short disease duration respond the best. If we need to prioritise subgroups that will benefit the most then I would recommend the following: 1) SMA type 1- with disease duration <12 weeks. This is because this subgroup response is better compared to those with longer disease duration and there is risk of prolonging difficulties for some of the severely affected children. 2) all pre-symptomatically diagnosed siblings 3) All Type 2 SMA with disease duration less than a year

Name	[redacted]
Organisation	
Role	Carer
Job title	mother/carer/teacher
Location	England
Conflict	No
Disclosure	
Comments	SMA affects quality of life for patients and families: Social affects. Our 5 year old son is unable to attend other childrens' birthday parties and social events if they are inaccessible or inappropriate (e.g.; soft play centres). He often cannot go to friend's houses or attend sleepovers due to steps, stairs, carpets and night-time care required. As a family we are limited to where we can go for days out, holidays and social events. Effect on siblings is also severe, but dependent upon how much additional support is available. If your child has had access to Nusinersen. Age 5, UK diagnosis severe Type 2, French appraisal strong Type 1. Symptomatic from 3-4 months. Treatment started at 4 years 2 months. No further weakening. Gained in strength and movement. HMF prior to treatment around 10. HMF 6 months after treatment 18. Score 18 maintained at 1 year. Slight curve to the spine has reduced. * Since treatment no hospital admissions. 4 admissions prior to Nusinersen. * Sleep patterns variable (from 1-6 wakes nightly) but significantly lower since treatment (usually 2) and now able to roll from side to side in bed. * Social opportunities are improved and broader due to increased stamina, reduced fatigue and improved confidence

	* Getting around is easier (no longer falls in car seat, can travel in wheelchair due to increased muscle function and improved head control). Able to manually propel lightweight wheelchair for longer and further indoors and manage outdoor use of power chair for a full day. * Mental well-being. Feels healthier, stronger and happier. Stronger voice and improved ability to communicate. Able to do more inclusive activities and achieve more on a personal level has improved confidence. Now able to eat publicly without fear of aspiration (inclusion at school lunch and eating at social events). Feels hungry, asks for food, less need for gastrostomy feed everyday. Caring responsibilities -mother, father, sibling, grandparents, 1:1 at school Treatment over 14 months, 7 doses. Physical milestones: -rolling prone-supine-prone -independent sitting with hands free -able to lift head prone on gradient wedge -raise arms to head

Name	[redacted]
Organisation	
Role	Granny
Job title	Retired Headteacher
Location	England
Conflict	No
Disclosure	
Comments	My grand-daughter has been diagnosed with Spinal Muscular Atrophy Type 2/3. Which, as you know, is a rare, inherited muscle -wasting disease. If untreated, she will, by the time she is about 10, be in a wheelchair, unable to move, breathe or swallow without aids, and be doubly incontinent, but still have a normal life expectancy, this will be such a waste of life and devastating for our family to watch her deterioration month by month and be powerless to do anything to prevent it. Spinraza/Nurinsen has been welcomed and funded by countries across the world including poorer countries such as Greece and Portugal who have been able to broker a deal with Biogen would are keen to come to a favourable financial arrangement with the NHS in England. I feel that the NICE report is flawed in many ways: A totally negative slant has been put on all of the evidence; It says that there is insufficient evidence of success while at the same time stating that the drug 'provided a substantial clinical benefit' and 'statistically significant improvement in motor function'; they stated that it was difficult to assess as there had been no deaths!; and that it would not be 'fair to people of all ages'! SMA is not fair. Neither is it fair to all children under 18 with SMA who, through no fault of their own, have developed this condition and have been refused treatment when other people with self-inflicted conditions such as obesity, drug and smoking related diseases etc are being treated with drugs agreed by NICE and paid for by the NHS. There are no other options other than Spinraza for my grand-daughter and others like her. Please, please agree to fund Spinraza for all under 18s in England.

Name	[redacted]
Organisation	
Role	Carer
Job title	
Location	England
Conflict	No
Disclosure	
Comments	My main concern is that you are heavily basing the fact that you will not recommend nusinersen due to the lack of evidence of long-term benefit coupled with the high cost. The long-term benefit should not be an issue as it is highly likely that other drugs which are going through clinical trials (e.g. AVXS-101, RG7916) will be more effective and less intrusive (as current results would lead us to believe) and therefore the administration of nusinersen should only be required in the short term to save lives and stop (or at least slow) the degenerative effects of SMA which studies have shown to be the case. Nusinersen is needed now not in the future!! In terms of cost it would seem that Biogen (from their press releases) are more than willing to discuss price structures which would hopefully satisfy all parties (although as NICE have given no real indication to us, the SMA community, on exactly what would constitute an acceptable cost this is hard to gauge). This also raises the question of why so many other European countries most with far less GDP per capita than the UK are able to provide this drug to those that need it? What deals have they managed to broker with Biogen that are acceptable to both? We should also consider the moral obligation that a tax funded institution (NHS) has to provide treatments that are available to treat a condition which is life threatening? In terms of the impact personally please consider the following if you are in any doubt of how destructive SMA is (although I would hope in order to come to your current conclusion you already understand the full implications of the effect of SMA on a person and their family and friends??): On a daily basis our son is affected by SMA as he requires help sitting up in bed, getting dressed, showering, preparing food, getting in and out of the car, the list goes on. Practically all of these things he could do 12 months ago. More recently he is having trouble swallowing and coughing, his life and his dignity are disappearing, shriveling before his and our eyes. He is, and has been for a while, on daily strong painkillers, salbutamol (which is having less effect over time) and St. John's Wort to try and boost his mood. He now has regular appointments with a psychologist who is trying to help him understand his condition and how to cope with it.

	He also tries to participate in physiotherapy but this is becoming more difficult for him and less effective. So just from this you can appreciate he is constantly utilising NHS resources especially when you start to add occupational therapy, physiotherapists, consultants etc .... things which may be alleviated or reduced if he was given Nusinersen. While you pontificate and make immoral decisions we sit and watch as our son gradually gets weaker and weaker, as his boundaries close in on him and his mental state deteriorates. This disease affects not only the patient but so many people around them as a recent study in Australia highlights (see https://bmjopen.bmj.com/content/8/5/e020907). Please re-consider your initial decision before more die and the lives of so many other for whom there is a real alternative through nusinersen become even more unimaginably difficult.

Name	[redacted]
Organisation	Yorskhire Children's Neuromuscular Service based at Leeds Children's Hospital
Role	NHS ProfessionalYorskhire Children's Neuromuscular Service based at Leeds Children's Hospital
Job title	Consultant Paediatric Neurologist
Location	England
Conflict	Yes
Disclosure	I am involved in delivering the [redacted] I have participated in an [redacted] I have participated in a [redacted]
Comments	On behalf of the Children's Neuromuscular service, based at the Leeds Children's Hospital and serving the population of North, East and West Yorkshire, we would like to register our concerns in relation to the NICE appraisal for Nusinersen. Whilst Spinal Muscular Atrophy is a rare genetic disorder, we see between 5-10 new cases/year in our region, the majority of whom have the most severe, early onset, type 1 form, associated with rapid, progressive muscle weakness and death in infancy. Therefore, sadly, we have been involved in supporting many families through the unimaginable trauma of watching their babies deteriorate and die. At the same time, we have managed many children with the milder type 2 and 3 forms of the disease as they lose their motor skills and require additional physical and medical care. For example, there are currently 5 children under 5 managed by our service, who did achieve independent standing and walking but who will lose this ability in the next year or so. These are otherwise bright children with normal cognitive functioning who will ultimately become dependent on carers for all their day to day needs with

	consequent negative effects on quality of life and social participation for the young person and their family. In this context, it has been exciting to witness the development of potential therapies for SMA and in particular to see the clear benefit of a gene modifying therapy (Nusinersen) in 2 international randomised controlled trials (Endear and Cherish). Conducting a robust trial in SMA is hugely challenging given the nature of the diagnosis, and in particular including a placebo arm that required 2 separately blinded teams on each trial site. The methodology and selected end points were clear and relevant in each trial and, appropriately, the trials were stopped at interim analysis when the significant difference in end points between treated and untreated groups were noted. The trials have both been published in highly respected peer reviewed journals and data from these trials and the other open label studies on Nusinersen have been scrutinised by both the EMA and FDA prior to approving a licence for the drug in Europe and the US. As a consequence, the drug is now available and in use across Europe, North America and has been approved for type 1 SMA in Scotland. We note that the NICE appraisal concluded that data was not available for a sufficient period to determine the long-term effectiveness of Nusinersen. Whilst this is true, and an inevitable consequence of the research governance of the trials, there is long term data available from the open label studies, from other international databases in countries where Nusinersen is available and from the Biogen sponsored extended access programme for type 1 SMA in the UK. Data from these sources suggest ongoing benefit from treatment over time, although it is also clear that early treatment confers significant benefits over and above delayed treatment. The UK SMA network has an established natural history database (SMA REACH) which collects standardised data akin to that used for outcome measurements in clinical trials. Thus, there is an existing framework for robust data collection in treated individuals which would serve to answer the question of the long-term benefits of treatment in relation to the natural history. We do not believe that the summaries of the clinical and cost effectiveness reflect the true burden of this disease. The standardised health utilities/modelling tools are designed to evaluate treatment benefits in older individuals and we do not believe they reflect the ‘costs’ in the SMA population, especially for infants and young children. In particular the models do not include the inevitable costs of progressive weakness in the type 2/3 forms of the disease - spinal surgery, respiratory support, educational and social care packages, or the effect on carers’ income and well-being when supporting a severely disabled child. Neither do they capture the costs of supportive treatment in an infant with type 1 SMA which, particularly in relation to critical care bed usage and hospital stays, are considerable. Given the availability of a disease modifying treatment, there is a sea change in expectation and approach to supporting infants

	with type 1 SMA. This is reflected in the recently updated international consensus statement on standards of care in SMA, a model of management that we would follow in the UK. A greater number of infants with SMA type 1 are now receiving intensive respiratory support with significant impact on resources both in hospital and in the community. In light of recent high profile legal cases where there was a discrepancy in expectation regarding parents and clinicians views of the infants outcome and potential effects of therapy, it is likely that families, and indeed clinicians, will find it extremely difficult to accept purely palliative/supportive care for infants with SMA as happened in the past. Thus, not choosing to support Nusinersen treatment in SMA is unlikely to be a more cost-efficient solution. We appreciate that the costs of treatment are high but would strongly urge the appraisal committee to review the trial data, in particular the significant benefits conferred by early treatment in infants with type 1 SMA from the Endear and Nurture studies, and in younger children with types 2 and 3 SMA in the Cherish study. We would strongly support a managed access agreement, similar to that between NHSE and PTC therapeutics for Translarna in Duchenne Muscular Dystrophy, to evaluate the role of Nusinersen in the SMA population in the UK. We believe that we have the structures in place in the UK; a strong and effective clinical network and a robust natural history database (SMA REACH), to provide meaningful data regarding the longer term effectiveness of Nusinersen in various SMA populations. Finally, we would ask the committee to consider how a family living in England and Wales should act if their infant is newly diagnosed with SMA type 1 once the Extended Access Programme is closed on 1st November. As you are aware, Biogen have agreed to support ongoing treatment for those already enrolled in the programme but will not support treatment for newly diagnosed cases. Many families will seek treatment in Europe or consider relocating to Scotland. This, of course, is only possible for the more affluent families and thus, in response to the final point regarding discrimination, we believe this decision will discriminate against those families with fewer means, typically in our region this will be the socially deprived South Asian population of West Yorkshire, where we have shown there is a 4.5 x greater chance of developing recessively inherited neuromuscular disorders like SMA. Approved and signed by: [redacted], Consultant Paediatric Neurologist [redacted], Consultant Paediatric Neurologist [redacted], Consultant Paediatric Neurologist [redacted], NM Specialist Care Advisors

	[redacted], NM Specialist Nurse [redacted], NM Specialist Physiotherapists [redacted],NM Specialist OT [redacted], Consultant Paediatrician with interest in Neurodisability [redacted] [redacted], Consultant in Paediatric Neurodisability, [redacted] [redacted], Consultant in Paediatric Palliative Care, [redacted] [redacted], Consultant Neurosurgeon, [redacted]

Name	[redacted]
Organisation	
Role	Carer
Job title	parent
Location	England
Conflict	No
Disclosure	
Comments	My daughter has SMA Type 2 , she was diagnosed at 16 months and is now 22 years old. We are devastated to hear that the only potential treatment which has become available which could make her life a little easier to live she has been denied access to by NICEs decision to not approve the drug. She was never given the opportunity to access the drug because of her age and her diagnosis Every minute of her day and night is affected by her condition since every function of her body has become progessively weaker over the years . the only part of her body which has remained completely unchanged is her brilliant brain. Every day for 22 years she has had to relie on her family to undertake all her personal care , hoist her from bed to wheelchair to loo to bath , dress her , brush her hair , prepare and cook all her food , cut it up for her , carry her bags , transport her to wherever she wants to go and remain with her since she is reliant on others. With very little muscle strength she uses all of her energies to sit upright , move her arms as much as she can (which is only a few centimeters forward) for the most simplest of tasks which all others would take for granted. She cant even open a packet of crisps.She realises this treatment would not enable her to walk again because the deterioration in her whole body is so extreme but the chance to be less reliant on carers to do the day to day tasks of life would do so much for her self esteem and her quality of life . To be able to increase her lung function which is now at 25 % would be enormous - not be reliant on using a cough assist machine countless times a day never mind the endless hospital appointments which has affected the whole family and other siblings. Given the opportunity to maybe regain a little bit of extra power and strength to someone who has very little to start with is enormous to them even though it seems miniscule to the rest of us , Put ourselves in her shoes , its hard but i will fight all the way for her to have access to anything and everything which could make her quality of life better and I sincerely hope the NICE , NHS and the drug company can come to an agreement to make this only treatment available for this life limiting condition available to all that need it .

Name	[redacted]
Organisation	
Role	Dad
Job title	
Location	England
Conflict	N/A

Disclosure	My little girl is wasting away in front of me; she will lose her ability to walk very soon.
Comments	I find the decision regarding the denial Nusinersen to people suffering SMA extremely disappointing. I feel that the evidence has not been fully appreciated and applied to real life cases; particularly to SMA type 3. The clinical evidence is compelling, conclusive and significant enough to demonstrate that the this drug has a marked effect on SMA type 3 in proving improved strength. The drug's genetic design is structured around splicing SMN 2, which SMA Type 3 people have more than other many other types of SMA (1&2). If Nusinersen was given to my 4yr old, SMA type 3, little girl, [redacted],it would allow her to gain the strength for independent living. As a type 3 she is a breath away from having the strength to toilet independently and move around just that little bit better; enough to afford an independent life. The promise of an independent life. She may never run for a bus, but she would be able to hold functionality to a point of independence. The cost benefits can be seen when we determine the high levels of intervention (operations and 24hr support) to a disease that takes away strength verses an independent life of an SMA type 3 with Nusinersen. I do not believe the evidence has been fully evaluated against specific SMA type profiles and the potential benefits this drug would deliver to a SMA type 3 child. The efficacy of this drug is beyond doubt with many countries in the world looking to safeguard their citizens with Nusinersen. The drug has virtually no ill effects whilst delivery increasing in strength across the range of indices. moreover, patients have been shown to continually improve their strength for as long as they are receiving the drug. As such, holding the view that the drug should be denied to people because of a lack of long term evidence is poorly constructed excuse for not releasing the drug to people that desperately need intervention. The UK is the 5th richest country on the planet and with other poorer country's finding arrangements with Biogen, i find it difficult to believe it is cost prohibitive. We have an NHS to provide health care and as normal citizens we pay into this system all our lives and have no other options to access this form of treatment, our little girl is in effect being sentenced to a long, slow, suffering demise. All of her life opportunities will be utterly spent whilst all along this drug can transform her world. I would urge NICE to reconsider; with particular focus on case by case access for those that the drug would allow for an independent life.

Name	[redacted]
Organisation	
Role	Carer
Job title	
Location	England
Conflict	No
Disclosure	
Comments	Before Spinraza Life Expectancy 2 years. Detrimental emotional impact on all family After Spinraza Longer life expectancy, bright future, hopes and ability to make plans, improved mental health of us all. Before Spinraza Unable to support his own head, little strength and movement in his limbs unable to socialise. Laid down most of the time. After Spinraza Controls his powerchair, holds his head easily. Independence, social skills, interaction with others. Before Spinraza Losing his swallow, inevitably would have needed a peg. After Spinraza Eats orally safely, enjoys mealtimes with family, learning to feed himself. Before Spinraza Required constant help to hold and support toys etc. After Spinraza Plays independently with toys, books, paints, learning to write. Before Spinraza Delay with speech After Spinraza Speech has developed inline with his peers, increase in volume, forming sentences. Before Spinraza Most of the time laid down unable to interact with others After Spinraza Enjoys nursery, baby groups, playing with other children, can easily turn his head and takes part in social situations. Before Spinraza Doubtful he would be strong enough to take part in school After Spinraza Starts mainstream school in two years. Before Spinraza Weak chest function, susceptible to chest problems. After Spinraza Development in respiratory function. No hospital admissions
Submission date	2018 09 04

Name	[redacted]
Organisation	
Role	Parent of a child with SMA Type 1
Job title	Parent
Location	England

Conflict	No
Disclosure	
Comments	Our Son [redacted] has Type 1 SMA and has been receiving Nusinersen since August 2017. We believe that this drug has had a significant positive impact on both [redacted] and our lives for the following reasons: 1. [redacted] deterioration has stopped and we have seen improvements in movement that we would not have expected to see in a child with type 1. 2. [redacted] has had no hospital admissions since starting Nusinersen despite having several chest infections - he is a lot stronger in his abilities to manage and fight these infections without intensive medical intervention. 3. In terms of movement, [redacted] has experienced increased movement in his fingers, hands, wrists, feet, head and facial expression all of which have contributed to his increased abilities to communicate and interact with the rest of the world. 4. [redacted] uses a ventilator when asleep and since starting to receive Nusinersen we have seen ongoing reduction in both his supportive pressures and also his reliance on his ventilator - [redacted] has recently managed a full night without ventilator support (under a sleep study environment) - something we never thought he would be able to do. 5. Due to [redacted] deterioration stopping and his condition becoming more stable this has significantly improved his quality of life. [redacted] increase in strength and resilience has meant he is able to go out more and enjoy quality time with his family including going on holiday for the first time. In addition, we are now in a position that we are looking at schooling for [redacted], again something we would not have even considered pre Nusinersen. 6. [redacted] lack of hospital admission has had a significant positive effective on his family as any period of admission is both stressful and incredibly difficult for us as a family unit ([redacted] has a twin Brother and elder Sister) 7. Since starting to receive Nusinersen [redacted] has become more energetic and less prone to lengthy periods of sleeping - this means [redacted] is more willing to engage in activities and now has more structure to his day as he has a regular sleeping pattern. 8. [redacted] can now sit upright (within a fully supportive seating system) for extended periods of time which is improving [redacted] posture and allowing him a different perspective on the world other than his usual prone position [redacted] is one of the lucky few to be receiving this life saving medication in the UK and though we fully appreciate the financial burden of this drug to the NHS the positive life saving outcomes must outweigh the cost. We hoped for a slowing in [redacted] deterioration, what we have experienced with Nusinersen goes far beyond our hopes and has potentially saved our son's life.

Name	[redacted]
Organisation	
Role	Parent & Carer
Job title	Parent to SMA Type2
Location	England
Conflict	No
Disclosure	
Comments	I am writing as a parent, our youngest son [redacted] was diagnosed with SMA Type 2 last November at 18 months. He turned 2 years at the end of May and during the last 6 months, we have seen a big decline in his ability to do things. Despite regular physio, hydrotherapy, Hippotherapy and purchasing numerous pieces of equipment to help his overall support, the degenerative state of this condition is stealing the ability for him to complete general daily tasks like brushing his teeth, holding his cup to drink and eating his food. His reach is now limited, he can no longer put his hands on his head for a sing a long to "head, shoulders, knees and toes. It's heartbreaking. Having recently been on holiday, sitting watching the significant difference between our two sons (We have a 6 year old son too, [redacted]) it's devastating and eats away at us daily. We have to sometimes restrict what [redacted] does as we don't want [redacted] to feel upset he can't do something - e.g going to a trampoline/Park play area. So [redacted] misses out, grandparents who care for [redacted] whilst I work part time have to travel to us as all the equipment is at our house that [redacted] needs and we can't afford to buy a 2nd or 3rd set for their houses too. It splits the family up, e.g on holiday, our eldest son was so keen to go down to a beach to the rocks pools (only accessible by steps) he went with Dad whilst I waited with [redacted] at the top in his powerchair- it was awful when he so desperately wanted to join his older brother. I am actually sat in a foreign country right now as I write this trying to get our son on a drugs trial whilst my partner and [redacted] are at home, how sad I shall miss [redacted] returning to school. It kills me. Why should we have to do this?! Tell me?! His need is 24/7, it's like having a new born baby that doesn't even sleep during the day (for you to have a little rest), he wants to learn, he wants to explore, he's not content with just a few toys as his brain is well and truly working but he requires help, pressing buttons, opening lids, reaching for things, turning pages, moving, lifting, getting comfy. It's utterly draining both physically and mentally but he never asked to be born with this. Everything is a battle to get equipment, to get adaptions made around the house, to get appointments booked, we have to fundraise, which doesn't sit comfortable with us, but we don't have any option. It's literally a full time job, filling out paperwork, attending appointments, chasing appointments, waiting in for equipment to be delivered, attending fundraising events, daily physio, weekly hydro, weekly hippotherapy, whilst still trying not to leave our eldest son out with fear he may feel neglected. We constantly carry around a whole weight of guilt, guilty we can't do more for [redacted], guilty that we have less time for

	[redacted], guilty people are sending donations to fund equipment for our son, guilty of we go out for the day as hoping people don't think we are spending the fundraising money, the list goes on... it's like handing your life over. I wish I could literally swap places with you decision makers for 1 week and put your family and children in this exact same situation, just to experience what this feels like- this is real for us and although I still keep feeling that this bubbles going to burst and I'm going to go back to 'normal' life soon. It actually has got worse, as we once had hope for a treatment for our son and that hope is drifting away, please don't let it go, please keep my hope alive and give my son treatment and an opportunity for a future. If [redacted] does not get treatment and soon, he will continue to deteriorate and will require care 24/7 for life, he will be literally paralysed. Have you truly added the cost effectiveness of giving treatment against how much it will cost the Country in care, equipment, prof appointments, DLA, Carers Allowance, DFG etc? More drugs are coming through and being trialled, but access should be given NOW! Treat all the patients with the known approved drug NOW!! Make that difference NOW!! The price may be high at the moment but it will not remain this high forever as new drugs are on the way! If countries all over the world are approving this, 20 in the EU alone, why can't we?! With the help of social media, we see families and patients benefiting daily from this drug, it's making such a huge difference to their lives. Whilst this is amazing to see and quite rightly the individuals are able to access it, but imagine how that make us feel as parents? This is what you could be like son if you had this treatment but unfortunately you can't as we live in England. I dread the day I need to explain to him, but that day is fast approaching. It hurts. I represented my country in front of the queen at The Royal Windsor Horse Show when I was younger, I have never felt so let down by my own country and this health system. Shame on you if you don't make the right decision. Don't put a price on my child's life? Would you for your own child?!

Name	[redacted]
Organisation	
Role	Carer
Job title	Director
Location	England
Conflict	No
Disclosure	

Comments	From a family with a 4 month old daughter who has recently been diagnosed with SMA Type1 my comments here relate more to the drug availability not the report. That said, I do believe these comment should be treated with equal value. I have read the document and understand the biggest factor here is cost. To be fair, finances pretty much structure and control most things within society at this present time. However the treatment Nusinersen has given our family something money can't buy and that is a feeling called 'hope' Now I don't know if this treatment will help our daughter or not but we will always be grateful that she will be given the chance to try and make the most of this treatment and show signs of improvement. What really hurts us as a family is knowing that in a few months time another family just like us are going to receive devastating news in a hospital meeting room that their child has been tested positive for SMA type 1. What hurts even more is they potentially will not be given the chance to hold onto the 'hope' that we are currently hanging on to each day.

Name	[redacted]
Organisation	
Role	Parent of Sma child
Job title	Electrician
Location	England
Conflict	No
Disclosure	
Comments	My son [redacted] Waterman is currently receiving Spinraza at Gosh for type type 1c SMA. he was lucky enough to be included into the expanded access program for a select group of children. Since receiving his treatment we have watched the transformation of a seriously weakening child to a thriving boy who has gained significant progress in his motor function and health we are continually amazed by his progress. He starts pre school in the coming weeks an achievement we never thought possible. With the right support and treatment children just like [redacted] will live a happy more fulfilled lifes. Since Spinraza we are excited for his future no mater what it intails. I think every child deserves a chance like [redacted]. I think this treatment should be available to everyone suffering from SMA despite of cost. [redacted]

Name	[redacted]
Organisation	
Role	Carer
Job title	
Location	England
Conflict	No
Disclosure	Parent
Comments	We have been taking our 13-year-old son, who has Spinal Muscular Atrophy Type 3a, overseas for Nusinersen treatment since March 2017 (when he was age 11). He has now had 7 lifechanging treatments. 1. Previously, without treatment Our son's growth spurts accelerated degeneration. His condition had caused degeneration to the point where he fell at least 2 times a day & on some days multiple times. If he fell in the middle of the room, he would crawl and drag himself over to a chair to assist himself up to climb up furniture to stand - such as a chair. This was often unsuccessful in which case he required assistance to get up from a parent / carer. He had become increasingly reliant on his wheelchair to get around, especially outside. He had become reliant on his parent or a carer to assist with activities of daily living such as dressing, putting on his socks, shoes and splints. His father would have to carry him upstairs if he had become too tired to crawl up or down. He had bilateral pronated flat feet, pressure areas and experienced pain. Before treatment our son regularly fell and collapsed which often resulted in severe pain. He had several bad falls where he could not weight-bear requiring A&E treatment. He has had

	metatarsal fracture and soft tissue injuries over the years from falling that have caused him to have difficulty and pain weightbearing. The emotional impact of the condition was such that each bad fall resulted in him being petrified that he would NEVER walk again. We were extremely concerned & anxious about our son having a bad fall that would result in a fracture. We had read about boys with SMA type 3 around our son's age that had sustained a fracture and after immobilisation never walked again. We feared and were anxious that if he lost the ability to walk and became wheelchair bound, with the exacerbation of SMA disease progression he would be at increased risk of more pressure areas, immobilisation leading to respiratory problems requiring Non-Invasive Ventilation, scoliosis, pneumonia, becoming bedbound and having swallowing problems. 2. Our observations following treatment Our son doesn't fall or collapse as he did before treatment. He can walk faster & further. His gait has improved & is much less 'waddling' we have video evidence. He now walks at least 1 mile a day. He uses his wheelchair less and less over time. He is able to walk further & faster with more stamina as he has continued treatment & does not fatigue as he did before treatment. He can cycle on the exercise bike, which was never a possibility, and this is getting better & faster with every treatment ' we have video evidence. Our son can now independently rise from the floor again & with each treatment he is becoming obviously better at this & stronger again we have video evidence. He is no longer reliant on his parent or a carer to assist with activities of daily living such as dressing, putting on his socks, shoes and splints. He can manage walking up and down stairs. After the loading doses his right foot developed an arch and he no longer develops pressure areas or pain. This has also enhanced his walking ability with a narrower base and less waddling gait. Nusinersen treatment has benefitted our son emotionally. He can feel he is becoming increasingly able and independent which is positively affecting his attitude to life. He is NO LONGER scared of losing ability and getting weaker. He is embracing life and is now developing without fear, he is becoming stronger, he has more stamina and he is developing and becoming MORE ABLE as he grows. He has a thirst for knowledge & life. He is exceptional in all subjects at school. He wants to study Law at Oxbridge. With treatment, our son will not face the future we feared.

3. Clinical evidence pre and following treatment

In December 2015 when he was 10-years-old, before Nusinersen treatment, he

- walked 301.5 metres in the 6-minute walk controlled test
- weight 38kg
- height 142cm.

After 7 Nusinersen treatments, in June 2018, he

- walked 350 metres in the 6-minute walk test
- weight had increased to 42.3kg
- height had increased to 154cm.

This 6-minute walk test result following treatment was contrary to our pre-treatment experience when our son's height and weight gains accelerated degeneration. Such a deterioration is confirmed by Montes et al (2010) confirm as the natural progression of untreated SMA Type 3.

4. Costs of Care

I have been gathering my own evidence on the incremental benefit of Nusinersen to our son.

Education

Our son goes to our local mainstream selective school where he is excelling academically and he is extremely sociable & popular. Our local authority have given me the costing for him to attend the nearest school for physically & neurologically impaired children. Without Nusinersen treatment, and with the predicted physical degeneration, he would meet the entry criteria.

- £22,800 per annum - transport costs
- £21,269.26 per annum school placement (based on 2017/18 prices).
- £44069.26 Total

Community Care

The 'lower care' community care costings I have received are:

- £18 per hour day care,
- £24 per hour night care,
- £30 per hour Sunday & bank holidays.

Total up to £161,856 per annum (taking into consideration 40 weeks term time)

For 'complex care', costs are:

- £38 per hour day care,
- £45 per hour night care,
- £54 per hour Sundays & bank holidays.

Total up to £307,584 per annum.

Other health related costs

These include equipment and hospital costs including Outpatient Department appointments & patient admissions. All of these costs could be avoided if our son could receive Nusinersen treatment at home in England.

5. Our future 'our son, our family and us as parents and carers

Our son could go on to be a high earning tax payer putting into the system rather than taking out. My beautiful, bright and fun

	child is at the centre of this and his future and quality of life has been completed disregarded with the decision not to approve Spinraza. Why is my child's life not important? SMA type 3a is a severe and debilitating disease without treatment. Nusinersen has transformed our son & our families' life. If Nusinersen is not recommended by NICE for SMA type 3a in England our family will have to break up leaving his brother, 2 sisters my husband and son's father behind in order for me to try and move abroad with our son so that he can access treatment. Our son loves his life in England. He enjoys school, has a great set of friends and a loving extended family surrounding him. He NEEDS Nusinersen treatment in order to live an independent life. With continued Nusinersen treatment our son can achieve his goals being independent with activities of daily living. He is now age 13 and he is becoming more confident & happier as he grows. With Nusinersen treatment he is NO LONGER TRAPPED in a degenerating body. Our son has a life & his future ahead of him as he deserves. Nusinersen has huge implications for our son's future and the future of our family. With continued Nusinersen treatment he can live an independent life, where I'm sure this exceptional student will have an exceptional career and be an absolute asset to our society. With Nusinersen treatment, his body is NOT degenerating but improving and he does NOT face a fearful future losing abilities and associated devastating sequalae & suffering due to SMA disease progression. To watch your child throughout their childhood increasingly struggle, suffer or be in pain as they grow is cruel & devastating. Our son's improved abilities have welcomingly led to decreased physical demands for us as carers. We are less anxious about his condition as he isn't falling and is generally doing so much better. With Nusinersen treatment our caring duties will continue to diminish. We can continue our careers and will not have to give them up to become full time carers for our son as we thought we would. Reduced caring responsibilities mean that family life has become easier and happier for all of us & of course most importantly for our son. With Nusinersen, disease progression has halted and we no longer have to watch our son continuously struggle as he once did, we are amazed at our son's response to treatment that has changed all of our lives and futures for the better. It is really difficult to articulate the profound effect this treatment has had on our family & our outlook for the future knowing that our son WILL NOT degenerate. My husband just started a new job in January 2018, he felt he could take on the new challenge. I too in January 2018 had a promotion. We wouldn't have taken on these new roles before treatment. 6. We desperately need NICE to recommend Nusinersen Without treatment our son will endure torture in the form of physical & mental suffering as SMA would rob him of his independence causing him to rely on a carer to assist with all activities of daily living 'including washing, dressing, toileting.

	There is no dignity in unnecessary degeneration that can be avoided with treatment. ALL of the SUFFERING can be avoided with continued Nusinersen treatment. We need our son to access Nusinersen treatment at home in England as soon as possible. As his SMA disease progression has halted & his abilities are improving, he will need to access other health services less over time. Yet without treatment, over time our son would require increasing Health & Social Care services. His health needs would become increasingly complex and costly to health and social care services as his abilities would degenerate and associated sequalae and suffering onset. All the available up to date evidence-based research demonstrates the efficacy of Nusinersen in all types of SMA. Nusinersen has been validated to be effective in SMA type 1, 2 & 3. Our son has SMA type 3a and we have our own video evidence, objective evidence from his local Physiotherapist & objective evidence from his UK specialist centre and Neurologist overseas that demonstrate his improvement with Nusinersen treatment. Please recommend Nusinersen for SMA types 3. This is a cost-effective treatment for the long term and lifechanging & life saving for the affected individuals and their families. We need NICE to recommend Nusinersen for SMA type 3a. Our son showed symptoms of low tone as an infant at 8 months assessed by a Health Visitor. Our son continued to develop slowly, falling frequently with many A&E attendances as a baby & young child. Our son didn't reach all his milestones but as he achieved the ability to walk very late he was classified as SMA type 3a on diagnosis. Before our son started Nusinersen treatment he presented very similarly to a stronger Type 2 SMA individual. There is such a huge spectrum within each type of SMA. In a scenario where SMA type 3a individuals like my son were denied Nusinersen treatment he would lose the ability to walk and physically degenerate to become like a SMA type 2 or SMA type 1 individual. Whereas SMA type 1 and 2 patients with treatment will get stronger and may achieve the ability to walk. All SMA type 1, 2 & 3 affected individuals deserve access to Nusinersen treatment. Any decision not to give treatment to type 1, 2 and 3 SMA would be perverse and discriminatory to only recommend for individual types, that is not a broad recommendation for type 1, 2 & 3. We are regular hard- working citizens who want our child's suffering and loss of function and ability to end now with ongoing treatment at home. Our son's positive response to Nusinersen treatment has had had a huge impact on our entire family. Our home is a happier place where we look forward to all of our futures and are not scared of him growing and deteriorating. In fact, we look forward what each new day brings and we are excited about what he can NOW DO. Please help my son by recommending Nusinersen SMA including SMA type 3a.

Name	[redacted]
Organisation	Neuromuscular team, Sheffield Children's Hospital
Role	NHS ProfessionalNeuromuscular team, Sheffield Children's Hospital
Job title	Paediatric Neurology Consultant
Location	England
Conflict	No
Disclosure	No
Comments	Dear Sir/Madam, I am writing to you on behalf of the Neuromuscular Team in Sheffield Children's Hospital regarding the outcome of the appraisal consultation on nusinersen. Our trust currently sees 14 children with SMA and 7 of them are in the nusinersen EAP program, and one due to start nusinersen therapy on EAP. We would like you to highlight to you our experience of the outcomes for patients with SMA1 receiving nusinersen in terms of their motor/functional abilities/respiratory and perceived quality of life of care givers. In our second part we would like to comment on the way this appraisal has been undertaken. In brief, our 8 patients were of varying ages (8-70 months) and abilities prior to nusinersen. From a motor function wise 3 are now stable sitters. As you know by definition SMA 1 children never achieve sitting. This we think is definitely an improvement in motor function. Furthermore one patient had improved in CHOP score by 23 points in just 18 months post treatment, and is able to kick his legs. There is also significant improvement in head control, upper limb strength and function in 3 of the 8 which leads to ease of feeding, play, ability to partake in social activities and family life better (e.g. going on family holidays as can now tolerate upright posture better). Family and carers find it easier to care for them as they have gained small but significant skills. As our patients have only at most been on nusinersen for 18 months, we believe they may continue to improve in their motor abilities and if not at least not decline. These children are now also able to communicate better. 4 are speaking louder and for longer (in sentences) and 1 is able to communicate better with facial expression and eye-gaze to his carer. One child is now able to put their hand up in class to ask and answer questions and this has resulted in a tremendous improvement in engagement within class and socially with peers. That particular child is also able to sit unsupported on the floor to play at 'circle time' with peers for short periods. The child's confidence has increased. There has been significant decrease in hospital admissions in two patients enabling access to respite care, potentially attend school and participate more in life. The other children did not show an increase in unplanned hospital admissions.

	Prior to nusinersen some children needed supplementary feeding via PEG because they were so slow at eating. They are now able to eat faster and manage larger quantities such that they now require less or no additional nutritional support. At the moment we have not noted any significant improvement in respiratory function but also at the same time have not noted a decline in this, which is the natural history of SMA. We take this as an improvement in what is expected from natural history. We have not noted any significant side effects related to nusinersen therapy. From our cohort it seems patients who are able to access treatment earlier AND are less affected will benefit the most. Thus we feel that 2 of our SMA2 younger children will benefit on nusinersen and so will SMA3 children diagnosed early. We would like to point out how nusinersen was not assessed as a Highly Specialised Therapy when only a few centres in UK are administering it. This is in comparison to cancer drugs which are administered to a larger number of patients but still deemed as a Highly Specialised Therapy by NICE. We feel this is unjust and that nusinersen should be appraised as a Highly Specialised Therapy. We are concerned that NICE has appraised nusinersen and deemed that it did not show long term evidence based on the CHERISH and ENDEAR study. The CHERISH study was terminated early due to significant difference seen earlier than expected. We find that drugs for other conditions e.g. multiple sclerosis also do not show long term evidence but have been approved by NICE. We feel that the data captured and appraised has not given nusinersen justice as certain fields were not considered such as frequency of hospitalisation, child's participation in life and activities, quality of life of care givers, and communication of patient. We appreciate these are difficult to quantify but feel that they are more meaningful to families and affected child. We appreciate that nusinersen may have been costed very highly by Biogen, but having a decision against this drug which has shown definite improvement in many areas for patients with SMA without negotiations would put research and healthcare in the UK at risk of falling behind other developed countries. It discourages investment in healthcare research in the UK, to the detriment of our patients. Sincerely, [redacted] on behalf of the Neuromuscular Team in Sheffield Children's Hospital, UK.

Name	[redacted]
Organisation	
Role	Grandmother and helper of a child with SMA Type 2
Job title	Retired
Location	England
Conflict	No
Disclosure	No
Comments	I am concerned that the NICE appraisal has major shortcomings. A letter written last month to NICE by [redacted] and NIHR Senior Investigator, UCL Great Ormond Street and Ros Quinlivan, Consultant in Neuromuscular Disorders, Medical Research Centre, National Hospital for Neurology & Neurosurgery and endorsed by clinicians across the country plus the three major SMA research/support charities in UK and Muscular Dystrophy UK asserted that the regular commissioning route is too inflexible for the appraisal of a drug such as nusinersen, and that it fails to provide an effective mechanism to respond to the needs of subgroups of children with devastating conditions such as SMA. The full letter is at http://www.smasupportuk.org.uk/files/files/Research/Nusinersen%20letter%20to%20NICE%2020_8_18.pdf Prof Muntoni and Ms Ros Quinlivan also criticise the time taken in producing the NICE appraisal. Section 3.1 I strongly support the patient experts' view that the classification system does not reflect the full extent of the condition within each Type. By way of example, I refer to a child classified as Type 2 merely because he was able to sit unsupported at 6 months; but he was never able to pull himself into a sitting position, let alone right himself when he flopped. Within a few months the child's ability to sit unsupported was lost. He has never crawled, receives nutrition and fluids by PEG and needs non-invasive lung support when at rest as well as at bedtime. He cannot stand; for mobility, he must be carried to his powered wheelchair. There are children of a similar age with Type 2 but at the other end of the scale whose symptoms are far less severe. Section 3.2 The emotional, physical and financial stresses on a SMA child's parents are enormous - on his mother as main carer, on his father as breadwinner, juggling between dealing with a responsible work position and helping at home as second carer. Referring to a child with SMA Type 2, the near-death episodes with respiratory problems necessitating emergency admissions, each of several weeks, have been particularly telling on both parents with the father taking holiday leave, unpaid leave and, on occasions, sick leave to be with the child in hospital. The child's teenage brother has also suffered owing to separations from his immediate family while his parents resided in hospital accommodation to be with the child. Nusinersen would undoubtedly have alleviated so much of this. Without nusinersen, the child's and the immediate family's lives will continue to be on a knife-edge with fear of the progression of the disease, fear of hospital emergencies, fear of ever diminishing mobility, fear of early loss of life.

	Section 3.18 Evidence shows that nusinersen halts the degenerative process of SMA and, when administered soon enough, to improve a range of outcomes important to the patient, especially including respiratory and swallowing problems. It is established that current treatments merely manage symptoms. When weighing up the cost effectiveness, we should consider the holistic cost of current treatments and all knock-on effects on the patient, his parents and siblings. Almost every problem encountered by SMA patients and family is specialised and 'specialised' inevitably means great expense, either to them or to the state, whether medical, mobilising, social opportunities, mental health, or merely dealing with everyday functioning. By way of example, a child with SMA Type 2, from the age of 2yrs and over a span of 3 years, endured 8 emergency hospital admissions for serious respiratory problems entailing stays in paediatric intensive care/high dependency of up to 6 weeks on each occasion. At least three (maybe more) of these emergencies necessitated paramedics/ambulance service. There have been, and still are, routine overnight studies, PEG operations, countless outpatient appointments with consultants, respiratory nurses, physios, nutritionists, GPs, OTs, and others; countless home visits by physios, respiratory nurses, NG nurses, PEG nurses, OTs, others; countless prescription medicines; a wealth of specialised disability and mobility equipment, specialised respiratory and physio machines, regular deliveries of feeding and respiratory supplies. The family home was modified to make it wheelchair friendly a local government grant was allocated; the remaining sum needed fell to the family to find. The mainstream pre-school playgroup which the child attended was allocated a grant for wheelchair access/accessible toilet and funding was provided for a one-to-one constant carer whilst he was there. The same carer is now with him constantly at mainstream school the school obtained funding for; also to create accessibility, in particular an accessible toilet/washroom with hoist. Motability was awarded to fund a large family vehicle to transport the child and his powered chair; there is also Parent/Carer Allowance and Funded Respite Care (when details have been finalised) If nusinersen is not administered, the child at approximately 10years old, will need an operation to insert rods in his spine to combat scoliosis; every few months he will return to have the rods lengthened to keep up with growth. When he has stopped growing, there will be a major operation. And so it goes on. Current treatments and endless ‘knock-on’ problems, not only for the patient but also for the immediate family, entail huge expenses for life ‘I don’t question that they’d be less than the cost of nusinersen but they could be set against the treatment cost with reasonable effect. If we suppose that the child had been administered nusinersen on diagnosis at 18months, and the progress of SMA had been halted, it could be expected

	that the best part of the expense of current treatments and 'knock-on' effects would have been eliminated. Section 3.19 In my opinion, NICE's preliminary recommendations discriminate against children and adults with disabilities caused by SMA. Nusinersen is an available disease-modifying treatment and if this is not approved for funding by NHS, those people with SMA will be committed to face progressive muscle loss, furthering their disabilities and huge difficulties in life, resulting in a life shortening outcome. As mentioned before, the letter to NICE from [redacted] and company, contains criticism of the length of time taken to produce the appraisal. This could also be considered discriminatory; urgent disease-modifying treatment is needed now, not later, to halt the progress of SMA. Again, I refer to a 5yr old child with Type 2 who, without availability of nusinersen on the NHS, will need scoliosis corrective surgery within the next few years. Lumbar puncture procedures are more difficult after such surgery. It seems discriminatory, not only to allow progressive disability, but also to jeopardise the possibility of being treated with nusinersen should it become approved. More importantly, without nusinersen, parents of babies born with Type 1 SMA face the prospect of death of their children before reaching their 2nd birthday. This, surely, is discrimination. NICE's preliminary recommendation would have a most adverse effect on those suffering from SMA . The children, in general, are noted for being bright and happy with a huge zest for life and destined to play positive parts in our community. If their disabilities could be halted or lessened, and they could live longer, they would play an even greater part.

Name	[redacted]
Organisation	
Role	Patient
Job title	
Location	England
Conflict	No
Disclosure	
Comments	Though I have already sent this by email to the project lead, I am submitting it here to as I have no confirmation that my email was received. The comment box is not big enough for my complete submission, so please use the multiple comments as one piece chopped into box-friendly parcels. To whom it may concern at NICE I was dismayed but unsurprised by your proposal not to recommend the use of Nusinersen in adults with Spinal Muscular Atrophy (SMA), given the need for more studies to be undertaken to demonstrate its efficacy. I was shocked by your proposal not to recommend the use of Nusinersen in children with Spinal Muscular Atrophy (SMA), given the body of evidence that shows the treatment has clear clinical benefits. Looking deeper into your decision making process, I remain shocked. Please find below a summary of my thoughts and some questions I would be keen to see answered. I look forward to your reply and would be happy to meet with you to discuss this further. Yours faithfully [redacted] Adult with SMA type II Question: By what processes does NICE take account of its duties as a public authority to act in a manner consistent with human rights? These children, like all children, have a right to life. I draw your attention to the UN Universal Declaration of Human Rights, Article 3:“Everyone has the right to life, liberty and security of person“.(UN, 1948) And also to the UN Convention on the Rights of Persons with Disabilities, Article 10: “Right to life States Parties reaffirm that every human being has the inherent right to life and shall take all necessary measures to ensure its effective enjoyment by persons with disabilities on an equal basis with others. ” (UN, 2006) These aspirations are realised through the Human Rights Act 1998, Article 2: “Right to life Everyone’s right to life shall be protected by law. No one shall be deprived of his life intentionally save in the execution of a sentence of a court following his

	conviction of a crime for which this penalty is provided by law."(Legislation.gov, 2018) Publicly available information from the Equality and Human Rights Commission states "Public authorities should also consider your right to life when making decisions that might put you in danger or that affect your life expectancy."(EHRC, 2018) NICE recommendations are used to influence real-world decisions and patient pathways; NICE has a duty under the HRA to act in a way that protects life. Nusinersen has been shown to protect the life of children with SMA. It is the first and only treatment of its kind designed to do so. Decisions which impact patient access to this drug affect these patients right to life. Despite this, the right to life does not appear to be not explicitly mentioned in NICE's consultation. If NICE were to not recommend a life-extending treatment without sufficient justification, NICE could be found to be not acting in accordance with the HRA. The NICE website does show that NICE is aware of its duties under the HRA, though offers little detail as to how it ensures it discharges them. From NICE'S EQUALITY OBJECTIVES AND EQUALITY PROGRAMME 2016-2020 (NICE, 2016) "The Human Rights Act 1998 8. When public authorities such as NICE carry out 'functions of a public nature', they have a duty under the Human Rights Act 1998 not to act incompatibly with rights under the European Convention for the Protection of Fundamental Rights and Freedoms. The Equality Act's public sector equality duty uses the same definition of functions of a public nature as the Human Rights Act 1998. The Human Rights Act places responsibility for ownership of human rights matters on every public body and employee and requires active consideration of whether decisions have any implications for human rights." ... "NICE's compliance with the Human Rights Act 35. NICE achieves compliance with human rights requirements primarily through: • a robust procedural framework for developing guidance • an equality analysis process that also looks at the situation of groups in addition to those who share the characteristics protected under the Equality Act • asking advisory bodies to satisfy themselves that their decision making procedure is fair and transparent, that decisions do not discriminate against a group that is not a legally protected group, and, if they do, whether that discrimination is legitimate

	“obtaining legal advice when an issue arises that could potentially lead to challenge.” Despite these assertions, the procedural frameworks (NICE, 2017, 2017, 2018) underpinning the Nusinersen decision do not appear to discuss how to make decisions which respect every individual's human rights, including right to life. Within the Nusinersen consultation document (NICE, 2018), there appears to be no explicit mention of human rights or right to life. In all human rights discussions, the needs of the individual must be weighed against the needs of collective. NICE's approach to this is to calculate the cost relative to the benefit; incremental cost-effectiveness ratios (ICERs) per quality adjusted life year (QALY). A very high cost treatment which did not have a significant effect on health related quality of life (HRQL) would have a large ICER per QALY. The inverse is also true. Funding very high cost treatments which have very small benefits is unsustainable, and so the wider economic picture must be balanced against the needs of an individual or group of people. Both must be carefully assessed and considered in a robust decision making process. In this case, we are establishing whether it would be financially sustainable for the NHS to give children with SMA access to the only life-protecting treatment of its kind. NICE's SOCIAL VALUE JUDGEMENTS, Principles for the development of NICE guidance, Second edition (NICE, 2008) states: “NICE has never identified an ICER above which interventions should not be recommended and below which they should. However, in general, interventions with an ICER of less than £20,000 per QALY gained are considered to be cost effective.” Question: What is the evidence based rationale behind this figure of £20,000 per QALY being used as a general guideline for cost-effectiveness? Question: Does this figure change with inflation? Does it change according to the financial realities of the NHS at the time of decision making? Given that the cost-effectiveness of Nusinersen is assessed through the ICER per QALY measure, it is important to ensure that the QALY measure is reflective of the individual experience of these patients and those around them. However, there does not seem to be a consistent definition of a QALY used across all NICE decision making. Measurement of quality of life of very young children has been pointed out in the Committee papers (NICE, 2018) as extremely difficult. Similarly, it was noted that the PedsQL may not be an appropriate tool to measure outcomes

	which matter to school-age children with SMA. The approach to collecting data about health related quality of life of these children focuses on adverse events (such as respiratory infections), hospitalisations, motor milestones (rolling, sitting, lifting objects...), and interviews with a small number of clinical practitioners. There is no publicly available summary of the interviews with the clinical practitioners. Though it is important to maintain doctor-patient confidentiality and to allow the clinical practitioners to feel they can speak freely without fear of public/media misinterpretation, the lack of transparency feels disconcerting. Request: NICE seek the permission of the clinicians to publish a bullet pointed summary of the key points. There appears to be no explanation of how the clinicians views and measured outcomes were converted to a numerical value; the QALY. Given the importance of the QALY to the ICER per QALY measure, and thus to whether or not children will be treated with Nusinersen, it is important that this calculation is transparent. Question: By what process was the information gathered converted into a QALY? NICE has compared Nusinersen against best case usual care (henceforth best possible care) to give a value for the ICER. This neglects to reflect the reality of the situation for children with SMA and their families. Many of the parent submissions talked of the difficulties associated with lifting a growing child, lack of sleep, getting the right equipment and making adaptations to the house. Best possible care would include steps to address these issues being taken by non-NHS bodies acting appropriately in a timely manner, providing and advising on equipment, housing, social care, respite and so on. The submissions you received reflect that this does not always happen smoothly. Best possible care is not the same as currently available care. Similarly, best possible care is not always delivered by the medical team around the child. Within the company submission (Figure 34 and surrounding discussion), it is acknowledged that the UK standard of care in practice is not the same as that in other countries, highlighted by data from Italy. The UK does not presently deliver the best standard of care, which has a significant impact on patient survival. This must be addressed outside of the present discussion. Given that best possible care is not uniformly experienced by children with SMA in the UK at present, it does not seem logical to use it as a direct comparator when looking at Nusinersen. The “Green Book”from HM Treasury (HM Treasury, 2018) sets out a suggested process by which options of how to spend public money can be appraised. It recommends looking at an option compared to business as usual (BAU). In this situation, that would be a model of care which takes into account gaps in

	provision and waiting times for equipment, advice, and treatment, and the effects this has on children with SMA and their families. Request: NICE produce a BAU model of care to use as comparator to Nusinersen. The decision on whether or not to recommend Nusinersen and any medical technology must happen through a process which is fair, transparent, and uniformly applied. I request that NICE not only review the decision to not recommend Nusinersen, but also review the process by which such decisions are made so to make it clearer how NICE carries out its duties. A final word on quality of life The submissions to NICE reflected the downsides of having SMA. However, it also seems important to mention that when health is stable, and the correct support is available, a good quality of life can be achieved. Here are some examples from adults with SMA: [redacted] (me): - 3 highlights from the past year: Seeing the Killers play live at the O2, meeting some of my heroes at London Comic-con in full cosplay with 2 of my best friends, meeting [redacted] - the highlight of the past month: Helping put together a last-minute surprise celebration for a family event complete with gold-edged invitations, and the looks on my rellys' faces as we laughed and ate and drank altogether for the first time in 4 years. - something you're looking forward to?: Finishing my Physics degree and possibly starting a Masters [redacted]: 3 highlights from the past year: "- visiting Egypt and my 4th continent. Being featured on the BBC about successful people. Launching a marketing agency." Highlight of the past month: "- driving again after 9 months" Something you're looking forward to: "- my next goal in excited to achieve is delivering a Ted talk" [redacted]: "Passed Year - 1. A few amazing concerts, Celine Dion, Steps and Taylor Swift at Wembley... 2. Taking on Coventry City Council regarding a potential massive cut to my care package, featuring in the Guardian and being on my local radio, my fight continues still ... 3. Finding out my daughter is pregnant, I'm to be a Nanny! Last month - the news I'm having a Grandson Future - to win my care battle and to guide and influence my grandson to be a true gentleman and achieve his dreams... which he will as he has a strong feisty Nanny by his side! [redacted]: "3 highlights from my year - being brave enough to give up work and spend more time with my family and my kids growing up.

	- having a lot more energy for the people that I love and doing things together not just 30 days a year. - Started Painting with my mouth, one day I would like to be able to do it for a living. Highlight of the last month - (probably more like the last 3 months) it's warm enough for me to walk the dog without hands stopping working. I bloody love the sun! Future - I would like to drive again, I used to drive 700-1000 miles a week commuting to London and living a life, had to give that up because I got too weak to do with confidence any more. Really need to get something to enable me to do that. [redacted] "-3 things you love doing/are proud of Career Positivity Home -3 things you wish you could still do that you used to Feed myself Wash myself Hold my phone to my ear -3 things you're scared of losing the ability to do Work Drive Socialise [redacted] "3 things you love doing/are proud of - Enjoying a social life, theatre, cinema, meeting up with friends and watching my granddaughter grow up. Having a (reasonably!) active, alert mind which can cope with what life throws at it, mentally at least. The fact that I have spent a good deal of my life working and living to the best of my ability despite SMA Type 3 doing its best to make it very difficult. 3 things you used to do that you wish you could still do Drive Wash myself Walk 3 things you're scared of losing the ability to do Speak Write Laugh References: UN (1948) The Universal Declaration of Human Rights. Available at http://www.un.org/en/universal-declaration-human-rights/ (Accessed 1 September 2018). UN (2006) Convention on the Rights of Persons with Disabilities (CRPD), Article 10 - Right to life. Available at https://www.un.org/development/desa/disabilities/convention-on-the-rights-of-

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Name	[redacted]
Organisation	
Role	Carer
Job title	
Location	
Conflict	
Disclosure	
Comments	It's is crucial that nice listen to the success stories for spinraza! This drug is saving life's and improving quality of life! Please see below Please find below details of [redacted] spinraza success... [redacted] had numerous hospital admissions multiple times each year and this had been since birth, since starting spinraza she's been admission free. We have been able to reduce her bipap pressures which were stuck on 18/10 for over a year she is now on 16/6 which has never been possible. She can now feed her self and enjoys more of a variety of foods (previously purée foods or peg feeds) her head control and arm control has increased massively she can now put a fork to her mouth and is learning how to use a knife and fork Her trunk is her greatly increased she can now lean and is less floppy. She has previously had a neck brace for her head flopping especially when in the car she no longer requires this. [redacted] quality of life has increased dramatically, she can play more with friends, hair and teeth brushing is easier and she is able to help, her confidence has increased at school playing with piers. We are so happy that she has gained on her chop test and the results have been outstanding. We were informed that [redacted] may not find any benefits with spinraza due to her age, we was happy to try and maybe maintain her abilities. I feel [redacted] has changed so much for the better and this has had a huge impact on the whole family. We regularly get people stating how strong [redacted] is looking and that she is doing new things at school. This drug is life changing for families as well as the child. We hope that other families are given the same chance as [redacted] has been given and improve their health and quality of life. If you require any further assistance please call me on [redacted] Kind regards [redacted]

Name	[redacted]
Organisation	The Robert Jones and Agnes Hunt Orthopaedic Hospital
Role	Consultant Paediatric Neurologist with a Specialty Interest in Neuromuscular Disorders. Visiting Professor Chester University
Job title	Clinician
Location	Shropshire
Conflict	
Disclosure	
Comments	Dear Colleagues **Re; Nusinersen treatment for SMA patients [ID1069]** As a clinician involved in the care and translational research of children with a devastating neuromuscular disease, spinal muscular atrophy (SMA), I would like to express my deep disappointment in this treatment not being funded or given a positive outcome following the consultation. Severely affected children with SMA1 (who never acquire sitting position and who typically die at a mean age of 9 months of life) are now being offered a therapy that – especially if initiated close to the onset of disease- can substantially improve their motor function as well as respiratory function, feeding and life expectancy. This treatment allows a proportion of affected children the ability to acquire the sitting position and in some cases to stand. This current treatment is only one of many being developed and in the pipeline, including gene therapy, for this condition. In my personal practice we have a number of children receiving Nusinersen (N=7) and in all of these children, we have seen significant improvements in their abilities and quality of life. All these children received the Nusinersen later than those who experienced the best scores in the studies, as diagnoses were not made early, however in all there have been improvements. This may be less fatigue and ability to hold head up; one girl who is already 6 years but received the Nusinersen was very weak, but since the treatment has improved with motor control and now has a stronger voice and has not needed hospital treatment at all in between her doses. For another child who was in ITU most of her life, since starting Nusinersen, has been at home in between her injections (which are 4 monthly) – she has not been this stable since she was born. I reviewed one of my patients last week, she is almost 2 years old (23 months) – she is now sitting independently, driving her own wheelchair, eats normally (No PEG tube) and does not

	need ventilation and each assessment is stronger and stronger. She started her injections at 8 months of age (so still relatively late compared to the study but still making huge progress). All these families are grateful for the extra time they have with their child but also the quality of time they have as they are stronger and more energetic. They are happy and are enjoying life. Whilst we do not know the long term outcomes of these children, neither do we for other such expensive treatments and cancer treatments. For those who are stronger with type 2 and 3 SMA, there may even be more strength achieved and less hospitalisation required which would potentially offset some of the cost from the type 1 SMA patient's requirements. There are many advances being made in the treatment of these rare conditions and at present this has been welcomed by the communities and it is encouraging to see our colleagues in America and Canada as well as the other European countries all funding this treatment, however the UK, whilst our children take part in the trails do not have access to the drug. As we become more insular and exit Europe, the pharmaceutical companies will realise the UK and NHS England will not fund the drugs once they are licenced. As a result they will begin to remove the funding, that we rely on, for research and the UK will see further deprivation in its healthcare as a result of this. I understand that these drugs are expensive and that there needs to be consideration for the ongoing costs, however all orphan drugs are expensive and for these rare diseases, the monies need to be reinvested to improve on the products and make them more effective. As a managed access programme (MAP) as in other drugs that we use, clinicians would be responsible for monitoring the effectiveness and benefit from the drug and as responsible clinicians we would not be continuing a drug that is not of benefit and at present think carefully when dealing with such children regarding the level care needed and benefit as well as best interest for that child. I hope that NICE and NHS England will re-consider its decision.

Name	[redacted]
Organisation	
Role	Parent of Sma child
Job title	
Location	England
Conflict	No
Disclosure	
Comments	Our daughter was diagnosed with SMA type 1 shortly before she was 8 months old and started the treatment shortly after. She slowly developed symptoms over the first six months until she suddenly became ill with pneumonia. She spent three weeks in intensive care before being transferred back to the local hospital where further tests were done and diagnosis was finally made. She was then transferred to Great Ormond Street Hospital where she was offered and started the Nusinersen treatment. At this time she was very weak and unstable with her breathing and was started on non-invasive ventilation (bi pap). I was staying in hospital throughout this time while our older daughter was looked after by her father and my mother who had to reduce their work hours. This was very distressing for us to be away from home and they made regular trips to the hospital. During the period of the loading dose treatment our little girl developed pneumonia again. Although she was in intensive care again she was off the ventilator within a few days. We believe she survived this because of the Nusinersen treatment. Since then she has become more stable and has been able to come home. At the time of discharge from intensive care it was thought she would require 24 hour bi pap and oxygen support. This has not been the case, she is not on oxygen and is having increasingly longer spells without the need for the bi pap during the day. Since her fifth treatment she has made gains with her movement and breathing. She goes out for walks every day and has been able to go to her sisters school fete and sports day etc. Without the treatment we would not have been able to be home together as a family and see our daughter laugh and play with her sister. Since her discharge our daughter has been able to do a still increasing number of things such as clapping, using her arms, copying noises. As a paediatric nurse I can see the significant improvements both professionally and as a mother. We feel it is so important that the treatment continues to help improve lives and help in the research to finding a cure. We are pleased our daughter has been given the chance to experience and enjoy life with this treatment and we are very concerned others may be denied this opportunity.

	Yours Sincerely [redacted] The little girl in the above letter is my granddaughter – my daughter's child. Without repeating what is written above I wanted to comment on the current situation regarding the decision by NICE to decline ongoing funding of Nusinersen as a treatment for SMA. My granddaughter was diagnosed with SMA type 1 towards the end of last year. The impact of this for me includes not only seeing my granddaughter so ill, but also seeing my daughter having to cope with this. It touches every part of life. We were given some hope that things could be improved with treatment with Nusinersen. As a former nurse and now psychologist I am concerned about the impact knowing there is a treatment for SMA but not being able to access it will have on families of those still to be diagnosed. Since my granddaughter was admitted to intensive care last September I have been travelling from Lincolnshire to London every week to support the family. Through access to the treatment my granddaughter has in approximately the last four months achieved a level of stability that has given the family a degree of normality back in their lives and allowed my daughter and granddaughter to return home. They were in hospital for about 9 months, which the little girl's older sister found difficult. Being home together has made a big difference to their lives. As a former specialist palliative care nurse working mainly with cancer patients, I am familiar with the use of QALYS. While I understand the use of benchmarks in the health environment, I would question their role in such a new and specialist situation, and as such would argue that Nusinersen be considered as a highly specialist treatment. Ongoing studies would provide data that could offer an opportunity to refine the understanding and management of SMA, especially type 1 as the usual limited life expectancy does not give scope for this. The treatment has I'm sure changed the course of the illness for my granddaughter. She undoubtedly now has a quality of life that allows her to engage with the world around her. We have witnessed the significant improvements that Nusinersen can bring, and have been grateful to have the chance to experience my granddaughter as the funny, lovely little girl she now is.

Nusinersen for treating spinal muscular atrophy [ID1069]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5:00pm on 05/09/18 **email: TACommE@nice.org.uk** /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):	[redacted] Evelina Children's Hospital Department of Paediatric Neurology – Neuromuscular Service Guy's & St Thomas' NHS Foundation Trust London, UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry s	[redacted] do not have any conflicts of interest to declare.

Nusinersen for treating spinal muscular atrophy [ID1069]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5:00pm on 05/09/18 **email: TACommE@nice.org.uk** /NICE DOCS

Name of commentator person completing form:	[redacted] *(joint statement)*

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Has all the relevant evidence being considered?** In our view the relevant evidence has not been sufficiently considered. In particular, there is no consideration given to the fact that a better response to treatment has been demonstrated when the treatment is given at an early stage of the disease. It is vital to acknowledge that in the clinical trials as well as in the Expanded Access Programme, children receiving treatment very often have well-established disease rather than being at a pre-symptomatic or early disease stage. There are sound scientific reasons why earlier treatment would be expected to show better clinical results. In our view it is essential to consider the impact of the treatment not only in children with SMA as a group, but also specifically in those who start treatment at an early stage of the disease.
2	**Concerns regarding the long-term effect of the drug.** Although we understand the committee's concerns regarding potential long-term efficacy of the drug in principle, the published data demonstrate that treated patients show continuing improvement. The long-term effects of the condition SMA are well understood, with early death in infancy in those with type 1 SMA; denying this group of patients an effective treatment on the basis of concerns about either possible long-term efficacy or long-term side-effects seems therefore illogical. Formal post-marketing surveillance is, however, essential to continue to understand the long-term benefits and identify any adverse effects.
3	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** We do not think that the tools used for this assessment (QUALY measurement) are suitable for the group of patients with a rare, devastating disease such as SMA.
4	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** We do not think that the provisional recommendations are suitable. The recommendations in their current form would deny the group of children with SMA access to the only currently available effective medical treatment. The option then for a child with SMA type 1 would be early death from respiratory failure, or, perhaps more likely nowadays, long-term ventilation pending ability to access treatment (during which time there would be deterioration and loss of motor neurons, likely to result in a less good response to subsequent treatment).

Nusinersen for treating spinal muscular atrophy [ID1069]

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5	**Are the boundaries between different subtype of SMA clear or blurred.** The boundaries between different subtypes of SMA, classified on clinical motor milestone grounds which all neuromuscular consultants are familiar with, are very clear. Although there are rare instances of children who fall at the boundaries between 2 subtypes, it is nevertheless possible for experienced neuromuscular consultants to determine the correct subtype. In general, the system used for the classification of SMA is probably one of the simplest classification systems used within clinical medicine.
6	**Requested comments on whether there is a clinically distinct subgroup of people in whom nusinersen is expected to have better efficacy.** There is a subgroup predicted not to respond: those with no copies of the SMN 2 gene (routinely established on genetic testing of any child with SMA). Those children at more advanced stages of the disease process would be expected to show less benefit.

Insert extra rows as needed

Nusinersen for treating spinal muscular atrophy [ID1069]

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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.

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

BIOGEN

Supplementary Appendix 1:

Additional Clinical Data

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Nusinersen (SPINRAZA®) for the treatment of 5q Spinal Muscular Atrophy

1.1 SHINE: Infantile-onset patients

Data from an interim analysis (cut-off date June 30, 2017) of SHINE in infantile onset patients has very recently been presented at the American Academy of Neurology (April 21-27, 2018), and is presented below.(1)

Summary of SHINE interim results for infantile onset patients (data-cut: 30th June 2017)

- Among patients who began nusinersen in ENDEAR and continued in SHINE, additional improvements in total and specific Hammersmith Infant Neurological Examination Section 2 (HINE-2) motor milestones, such as head control and sitting, along with general motor function as measured by the Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders (CHOP INTEND) occurred in SHINE. The median time to death or permanent ventilation was 73 weeks.

- Among patients who received sham control in ENDEAR and began nusinersen in SHINE, new improvements in total HINE-2 motor milestones and general motor function as measured by CHOP INTEND occurred in SHINE. Within ENDEAR, the median time to death or permanent ventilation was 22.6 weeks among patients who received sham control. Within SHINE, 58% of patients who were alive without permanent ventilation at baseline and began nusinersen in SHINE remained alive without permanent ventilation at the data cut-off.

- Among those who were protocol-defined responders at the last available assessment for motor milestones and general motor function, some of them were achieved as late as day 578 and 818, respectively. Supporting that some patients may take considerable time to respond to therapy.

- The safety findings were consistent with those previously reported for nusinersen.

- These interim data further support the favourable benefit-risk profile of nusinersen in patients with infantile-onset SMA, and demonstrate that improvements in motor milestones can be achieved regardless of age at treatment initiation, although the benefits are greatest with early treatment.

- Further analysis of SHINE data will provide additional information on the long-term safety/tolerability and efficacy of repeated nusinersen doses across multiple SMA populations.

A total of 89 patients transitioned from ENDEAR, 65/81 previously randomised to nusinersen and 24/41 to sham control. Baseline characteristics are shown in Table 1. Patients who received nusinersen for the first time in SHINE had 2 *SMN2* copies (except 1 patient), a median age of 18 months, and a lower mean CHOP INTEND score at baseline in SHINE compared with those treated with nusinersen in ENDEAR.

Table 1. SHINE: Infantile-onset patients: Baseline characteristics

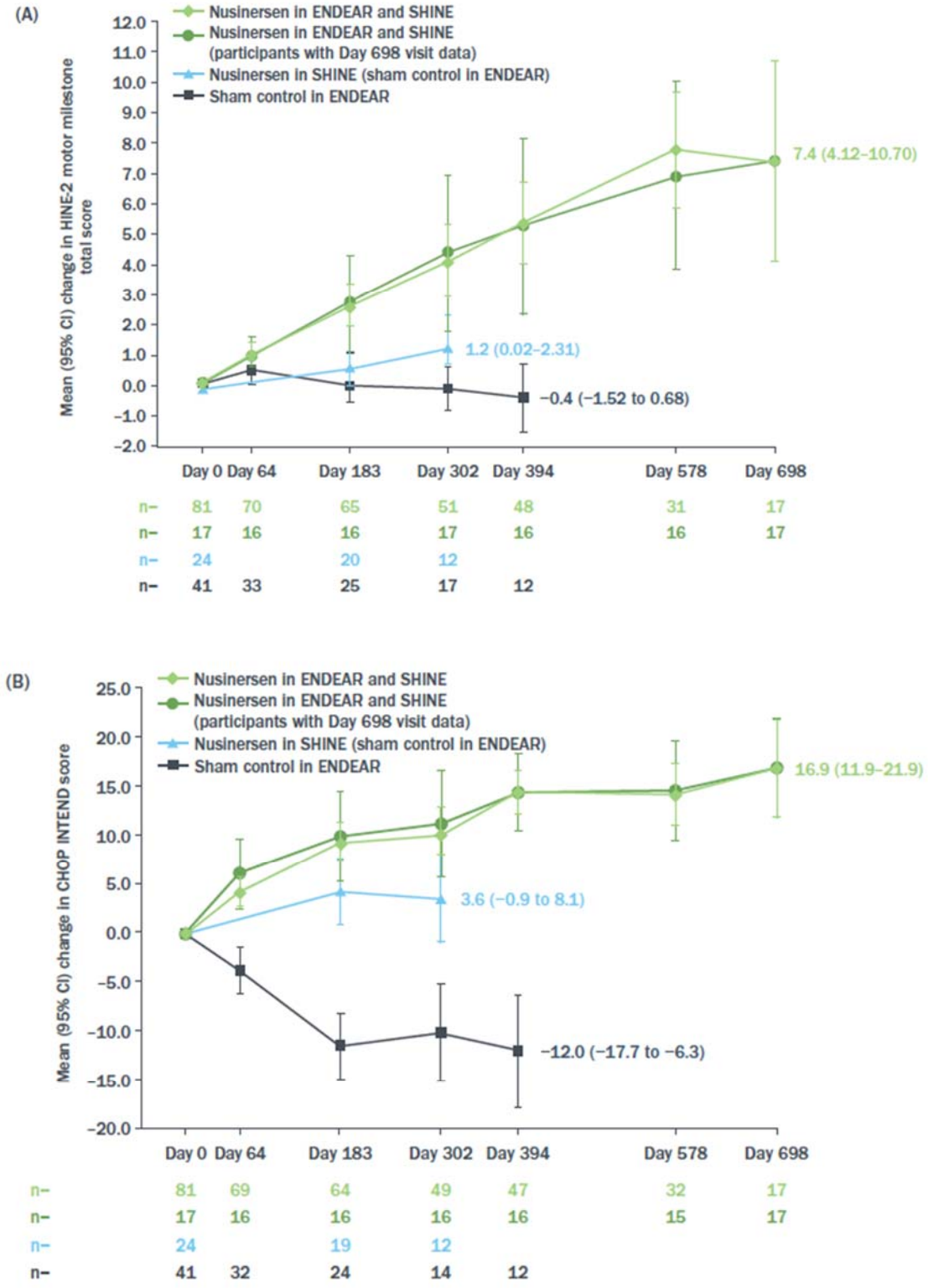
Characteristic	Sham control in ENDEAR n=41	Sham control in ENDEAR and nusinersen treated in SHINE n=24	Nusinersen treated in ENDEAR and SHINE n=81[a]
Female, n (%)	24 (59)	15 (63)	44 (54)
Median (range) age at first dose, mo	6.7 (1-9)	17.8 (10-23)[b]	5.4 (2-15)
Median (range) age at symptom onset, mo	1.8 (0-5)	2.1 (1-5)[c]	1.6 (0-4)
SMN2 gene copies, n (%)			
2	40 (98)	23 (96)	81 (100)
3	1 (2)	1 (4)	0
Mean (SD) total HINE-2 motor milestone score	1.5 (1.29)	1.4 (1.28)	1.3 (1.08)
Mean (SD) CHOP INTEND score	28.4 (7.56)	17.3 (9.71)	26.7 (8.13)

Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination Section 2; SMN, survival motor neuron; SD, standard deviation;
[a]One infant randomised to receive nusinersen in ENDEAR was not dosed, but was dosed in SHINE
[b]Median in the 12 participants who were alive and without permanent ventilation at baseline in SHINE was 16.8 (range 10–23) months
[c]Median in the 12 participants who were alive and without permanent ventilation at baseline in SHINE was 2.2 (range 1–5) months
Source: Castro 2018(1)

Overall, among patients who began nusinersen in ENDEAR and continued in SHINE, additional improvements in total and specific HINE-2 motor milestones, such as head control and sitting, along with general motor function as measured by CHOP INTEND occurred in SHINE; in those who received sham control in ENDEAR and began nusinersen in SHINE, new improvements in total HINE-2 motor milestones and general motor function as measured by CHOP INTEND occurred in SHINE.

The mean (95% confidence interval [CI]) change from baseline in HINE-2 total score and CHOP INTEND score over time is shown in Figure 1A and B. The mean (95% CI) change in HINE-2 total score from nusinersen initiation to last observed visit was 1.1 (0.20–1.90) for patients who received sham control in ENDEAR and nusinersen in SHINE (n=20/24) and 5.8 (4.58–7.04) for those who received nusinersen in ENDEAR and SHINE (n=74/81; pooled ENDEAR/SHINE data). NB, these data are based on the last observed visit available for each participant, including those who died or discontinued treatment.

Figure 1. SHINE: Infantile-onset patients: Mean (95% CI) change in (A) HINE-2 total score and (B) CHOP INTEND score over time[a]



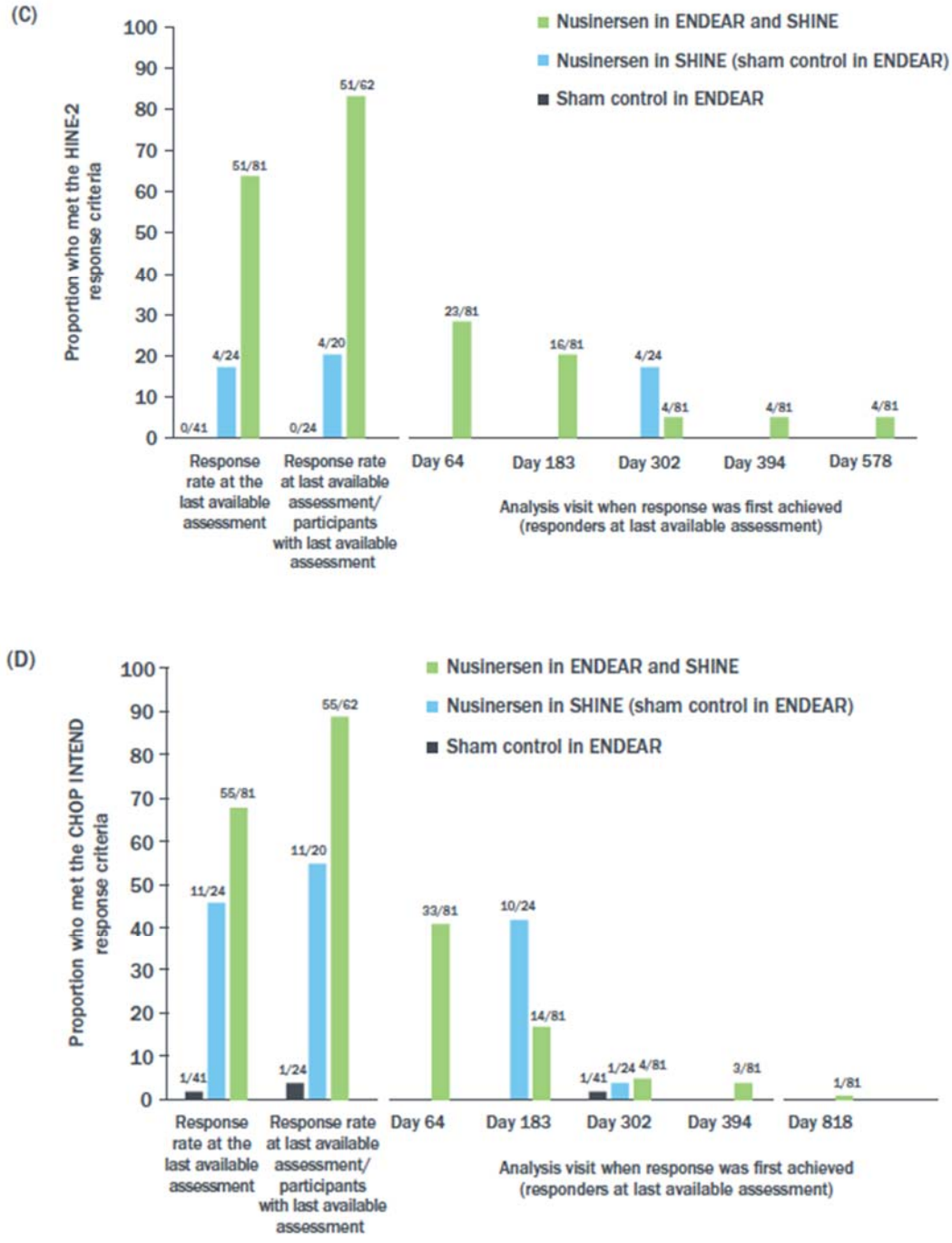
Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination Section 2

[a]Denominator is the number of participants with a value windowed to the analysis visit. Results displayed where n>10

Source: Castro 2018(1)

The proportions of patients achieving the HINE-2 or CHOP INTEND score (defined as ≥4-point improvement for CHOP-INTEND) response criteria at the last available assessment are shown in Figure 2. Among those who were protocol-defined responders at the last available assessment for motor milestones and general motor function, some of them were achieved as late as day 578 and 818, respectively.

Figure 2. SHINE: Infantile-onset patients: Proportions of participants who met the (C) HINE-2 and (D) CHOP INTEND score response criteria



Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination Section 2

HINE-2 response defined as: ≥2-point increase or achievement of touching toes in ability to kick, or ≥1-point increase in other 6 categories excluding voluntary grasp; improvement in more categories than worsening, where worsening was defined as ≥2-point drop or decrease to no kicking in ability to kick, or ≥1-point decrease in the other 6 categories
CHOP INTEND response defined as a ≥4-point improvement; participants who died or who were withdrawn during the study were considered non-responders
Source: Castro 2018(1)

For patients who received nusinersen in ENDEAR and SHINE, 23/81 (28%) had achieved full head control and 12/81 (15%) independent sitting as their highest motor milestone (overall cohort; at the last available assessment); no patients had yet achieved standing unaided or walking independently, although patients were gaining HINE sub-milestones in both categories. The percentages of patients who received nusinersen in ENDEAR and SHINE and achieved full head control and independent sitting at different study visits (based on patients who attended those study visits only) are shown in Table 2.

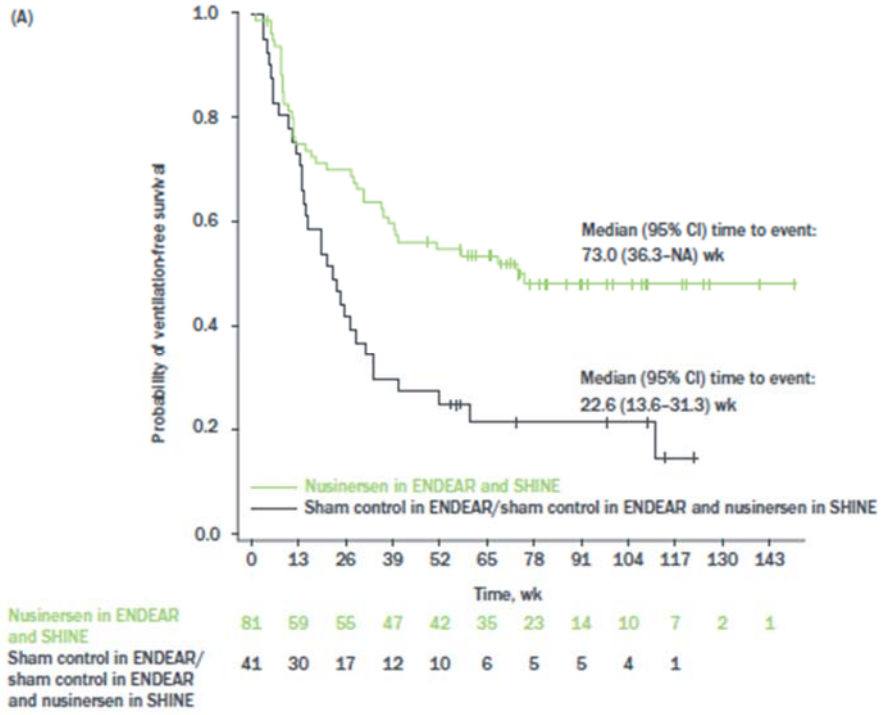
Table 2. SHINE: Infantile-onset patients: Percentage of infants achieving full head control and independent sitting over time

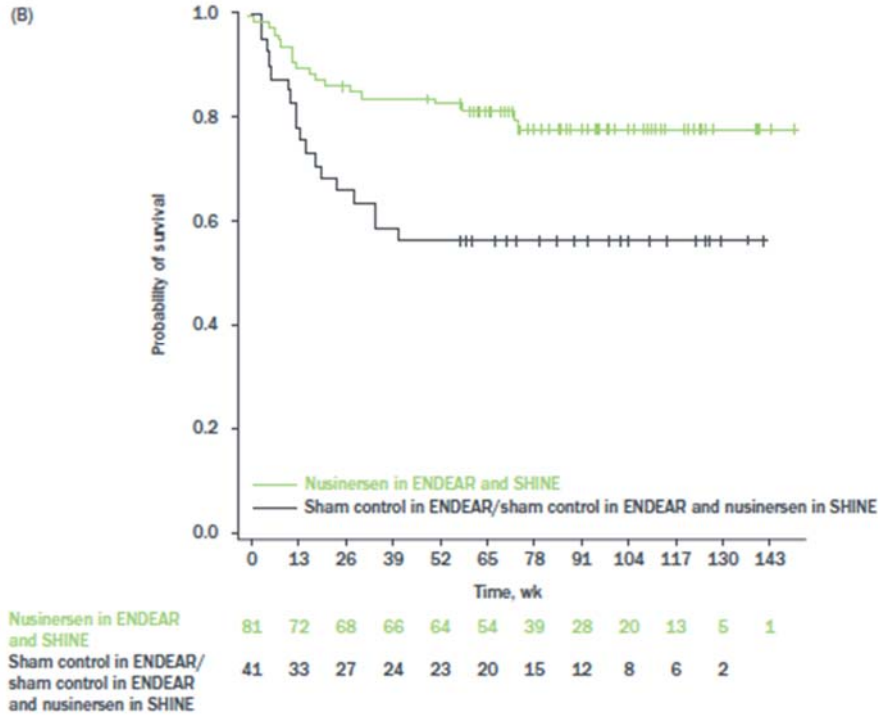
Study day	% achieving full head control[a]	% achieving independent sitting[a]
Baseline n=81	0	0
Day 64 n=70	7	1
Day 183 n=65	17	5
Day 302 n=51	25	10
Day 394 n=48	33	15
Day 578 n=31	45	29
Day 698 n=17	35	24

[a]The percentage is calculated based on the available data within each visit; participants who received nusinersen in ENDEAR and SHINE
Source: Castro 2018(1)

Time to death or permanent ventilation and time to death (starting from ENDEAR) are shown in Figure 3. The median time to death or permanent ventilation in patients treated with nusinersen in SHINE and ENDEAR was 73.0 (95% CI, 36.3–not available) weeks, and 22.6 (95% CI, 13.6–31.3) weeks in those who received either sham control in ENDEAR or sham control in ENDEAR and nusinersen in SHINE. Of the patients who received sham control in ENDEAR and nusinersen in SHINE (n=24), 12 were alive without permanent ventilation at baseline in the SHINE study. Of these 12 patients, 7 (58%) were alive and without permanent ventilation at the time of the data cut-off (median time on study in SHINE: 9.2 months).

Figure 3. SHINE: Infantile-onset patients: (interim analysis: data-cut: 30th June 2017) (A) Time to death or permanent ventilation and (B) time to death





Abbreviation: N/A, not available

Please note on figure 6 ENDEAR Sham patients on these graphs initially did not have therapy until after 52 weeks of being on trial, at which point they transitioned to nusinersen therapy on SHINE. Data from ENDEAR and SHINE are displayed in figure 6.

Source: Castro 2018(1)

The safety findings were consistent with those previously reported for nusinersen.

In conclusion, these interim data further support the favourable benefit-risk profile of nusinersen in patients with infantile-onset SMA and demonstrate that improvements in motor milestones can be achieved regardless of age at treatment initiation, although the benefits are greatest with early treatment.

1.2 ENDEAR: Hospitalisations in infants with SMA

Number and length of hospitalisations during ENDEAR were tertiary endpoints conducted in the subset of infants with the opportunity for a 6-month assessment. Tulinius et al 2018 has reported on the number and length of hospitalisations experienced by all patients in ENDEAR who were randomised and received ≥1 dose of study treatment or sham procedure i.e 80 infants (age, 32–210 days) who received nusinersen and 41 (age, 20–211 days) who received sham procedure.(2)

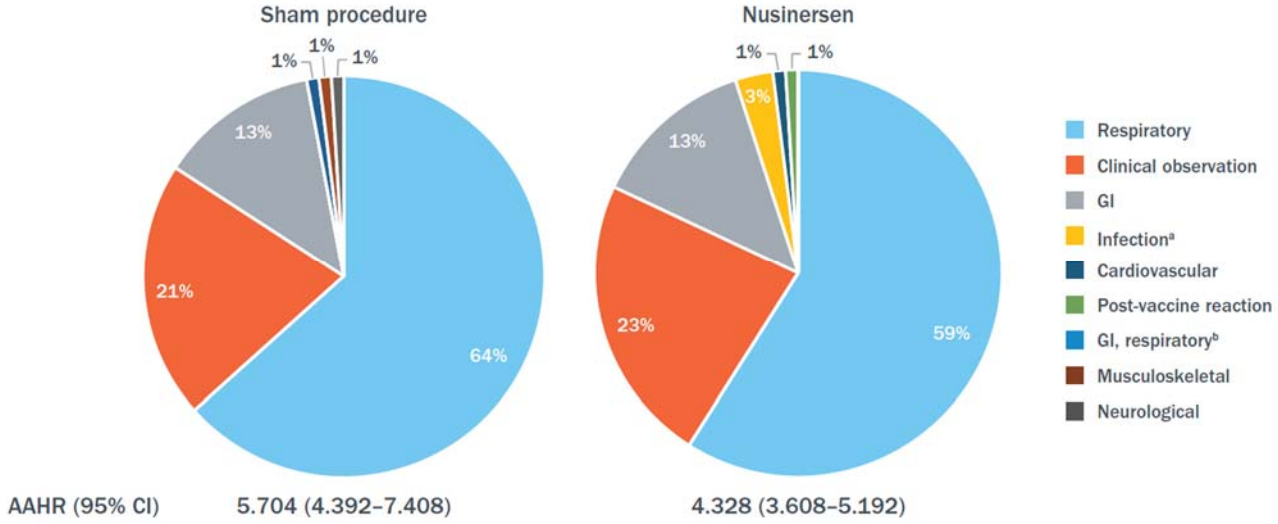
Hospitalisation was defined as an admission of >24 hours to a medical facility and was summarised using the rate at which hospitalisations occurred to account for differing sample sizes and follow-up lengths between groups. A post hoc analysis was performed to investigate the reasons for hospitalisation where reasons were categorised.

A higher percentage of infants in the nusinersen group had respiratory issues and needed respiratory support at baseline compared to sham (26% vs. 15%, respectively). The clinical trial was unblinded earlier due to a statistically significant benefit of being on therapy. This provided a shorter time for therapy to show differentiation of natural history vs sham on parameters of hospitalisation. The trial was not primarily designed or powered to show significance on hospitalisation rates. Clinical trials in paediatric rare disease limit the number of patients that can be recruited for investigation. Infants with SMA are more likely to require hospitalisation during winter months opposed to summer months, which could potentially add further confounders to data.

Despite all of the above there was a lower amount of time required in hospital for infants on nusinersen compared to those receiving sham.

Reasons for hospitalisation were similar between groups and mainly due to respiratory-related events (Figure 4).

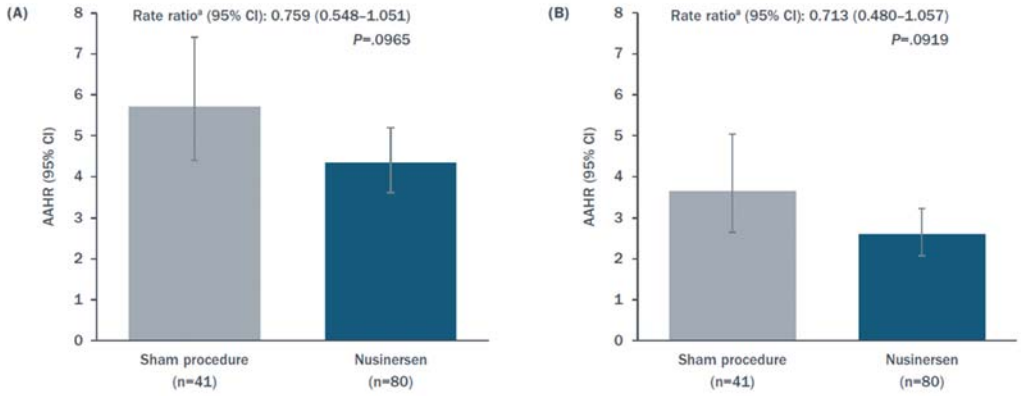
Figure 4. ENDEAR: Reasons for hospitalisations



Abbreviations: AAHR, adjusted annualised hospitalisation rate; CI, confidence interval; GI, gastrointestinal
[a]Outside respiratory tract; reported by investigators as: abscess at tracheostomy site (n=1), fever of unknown origin (n=1), urinary tract infection (n=1), suspected skin infection (n=1), fever (n=3), high fever (n=1)
[b]Combined GI and respiratory reasons
Source: Tulinius 2018(2)

The adjusted annualised hospitalisation rate (AAHR) trended lower overall and for respiratory-related hospitalisations in the nusinersen group compared with the sham procedure group (P=0.0965 and P=0.0919, respectively; Figure 5).

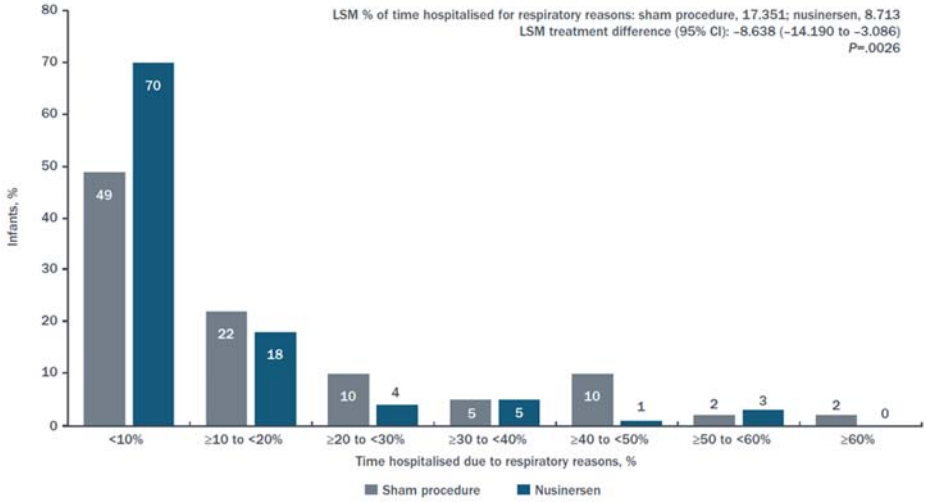
Figure 5. ENDEAR: Adjusted annualised hospitalisation rate (A) overall (B) for respiratory reasons



Abbreviations: AAHR, adjusted annualised hospitalisation rate; CI, confidence interval
The AAHR was based on a negative binomial regression adjusted for age at symptom onset and disease duration at screening
[a]Nusinersen/sham procedure
Source: Tulinius 2018(2)

Overall time spent hospitalised was significantly lower in the nusinersen vs. sham procedure group (least squares mean [LSM]: 0.114 vs. 0.207; LSM treatment difference [95% CI]: –0.093 [–0.151 to –0.034]; P=0.0022). LSM proportion of time spent hospitalised for respiratory reasons also was significantly lower in the nusinersen vs. sham procedure group (nusinersen: 8.713%; sham procedure: 17.351%; LSM treatment difference (95% CI): –8.638% (–14.190 to –3.086, P=0.0026; Figure 6).

Figure 6. ENDEAR: Proportion of time spent hospitalised for respiratory reasons during the study



Abbreviations: CI, confidence interval; LSM, least squares mean
Hospitalisation length was calculated as the mean proportion of time spent hospitalised during the study, reported as least square means (LSMs) based on analysis of covariance adjusted for age at symptom onset and disease duration at screening.
[a]Nusinersen/sham procedure
Source: Tulinius 2018(2)

In conclusion, nusinersen-treated infants spent significantly less time hospitalised overall as well as significantly less time hospitalised for respiratory-related reasons compared with sham procedure–treated infants.

1.3 ENDEAR: Ventilation support in infants with SMA

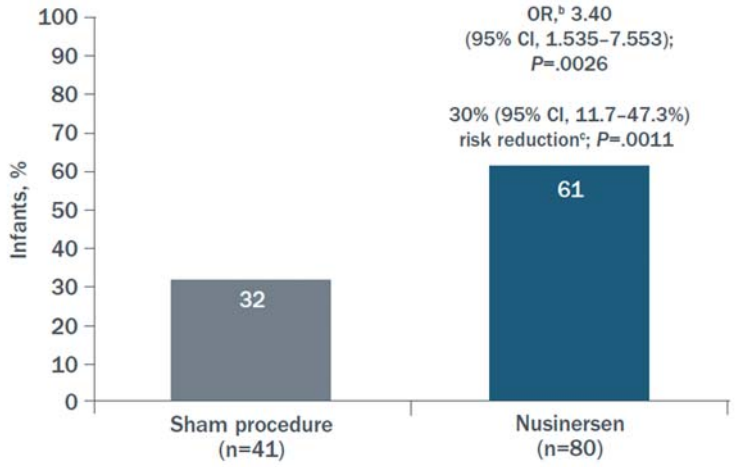
Parsons et al 2018 reported on respiratory outcomes, including ventilation support, permanent ventilation, and serious respiratory adverse events (AEs), in infants treated with nusinersen or sham procedure in ENDEAR.(3) Ventilator or bilevel positive airway pressure use (hours/ day) was recorded daily in ventilator diaries maintained by the infants' caregivers for the study duration. Permanent ventilation (determined by a blinded, central, independent endpoint adjudication committee) was defined as tracheostomy or ≥16 hours of ventilation support per day continuously for >21 days in the absence of an acute reversible event.

At baseline, all infants in both treatment groups did not require permanent ventilation, and 74% of nusinersen- and 85% of sham procedure–treated infants did not require ventilation support (≥1 hour/day). It should be noted that spirometry is not possible in infants as they cannot exhale at peak capacity on command. Number of hours of ventilation is subjective and severely confounded. ENDEAR was not powered to fully overcome this confounding. There has been a move to take a more aggressive (proactively higher ventilation settings and times) in all SMA patients in the recent past(4) but it is not clear how many centres have adopted this approach.

A significantly higher proportion of nusinersen- vs. sham procedure–treated infants survived without permanent ventilation at the end of the study (odds ratio [OR; 95% CI], 3.40 [1.535–

7.553]; P=0.0026; Figure 7). Treatment with nusinersen resulted in a significant reduction in risk of requiring permanent ventilation (30%; P=0.0011) compared with sham procedure (Figure 7).

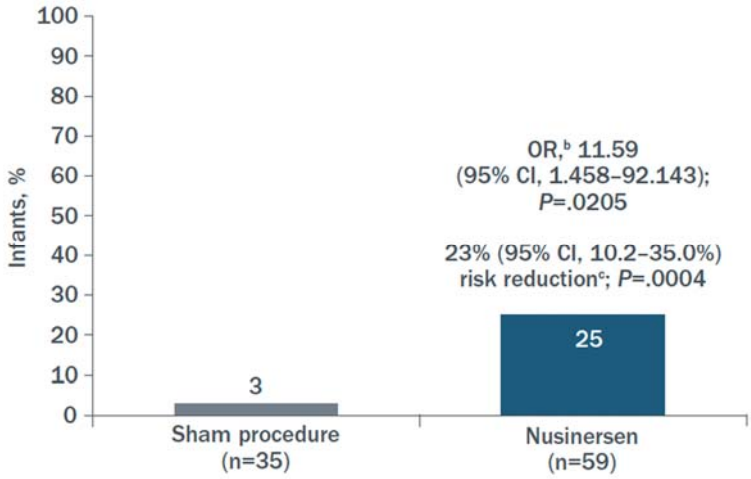
Figure 7. ENDEAR: Proportions of infants alive and NOT on permanent ventilation at the end of the study[a]



Abbreviations: CI, confidence interval; OR, odds ratio
[a]Among all infants randomised who received ≥1 dose of nusinersen or sham procedure. Based on post hoc OR analyses
[b]Ratio of nusinersen / sham procedure
[c]Difference of nusinersen – sham procedure
Source: Parsons 2018(3)

Among infants not receiving ventilation support at baseline, 25% of nusinersen- vs. 3% of sham procedure– treated infants did not require initiation of ventilation support while on study (OR [95% CI], 11.6 [1.5–92.1]; P=0.021; **Error! Reference source not found.**). There was a 23% (95% CI, 10.2–35.0%; P=0.0004) absolute reduction (nusinersen – sham procedure) in risk of requiring any ventilation support among surviving infants who did not receive ventilation support at baseline.

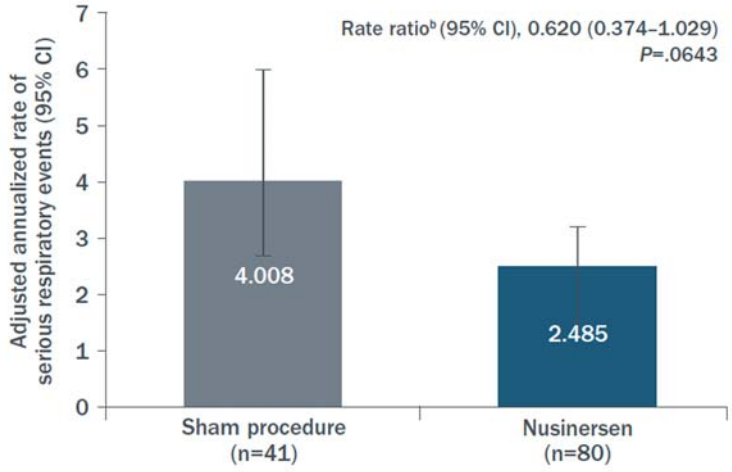
Figure 8. ENDEAR: Proportion of infants alive and NOT on any ventilation support at the end of the study[a]



Abbreviations: CI, confidence interval; OR, odds ratio
[a]Among infants not receiving ventilation support at baseline. Based on post hoc OR analyses
[b]Ratio of nusinersen / sham procedure
[c]Difference of nusinersen – sham procedure
Source: Parsons 2018(3)

The adjusted annualised rate of serious respiratory AEs also trended lower among nusinersen- vs. sham procedure–treated infants (P=0.0643; Figure 9).

Figure 9. ENDEAR: Number of serious respiratory events during the study[a]

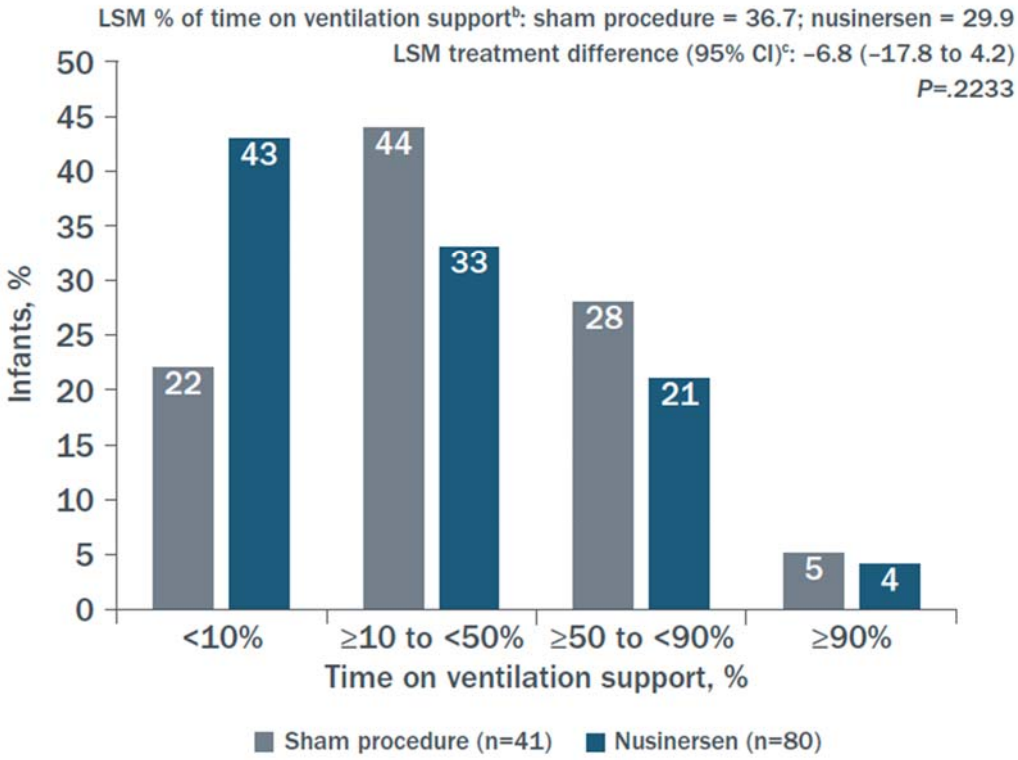


Abbreviations: CI, confidence interval
The adjusted annualised rate is the total number of events that occurred for all infants during the course of the study divided by the total number of subject-years of follow-up, adjusted for age at symptom onset and disease duration at screening based on negative binomial regression
[a]Among all infants randomized who received ≥1 dose of nusinersen or sham procedure
[b]Ratio of nusinersen / sham procedure
Source: Parsons 2018(3)

While a greater proportion of nusinersen- vs. sham procedure–treated infants required ventilation support at baseline, the LSM proportion of time on ventilation support trended lower

in the nusinersen group vs. the sham procedure group at the end of the study (P=0.2233; Figure 10).

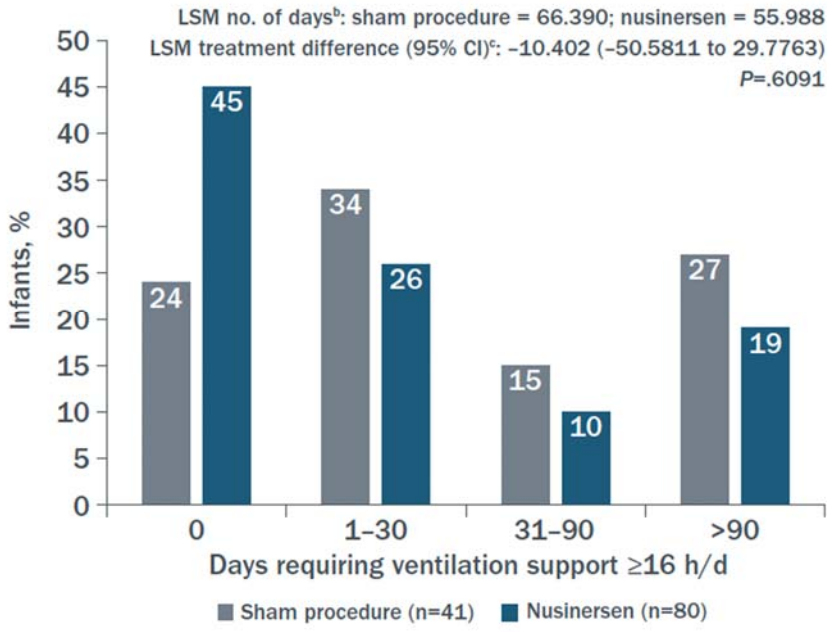
Figure 10. ENDEAR: Proportion of time on ventilation support at the end of the study[a]



Abbreviations: CI, confidence interval; LSM, least squares mean
[a]Among all infants randomised who received ≥1 dose of nusinersen or sham procedure
[b]Based on analysis of covariance adjusted for disease duration at screening and age at symptom onset
[c]Difference of nusinersen – sham procedure
Source: Parsons 2018(3)

Though not statistically significant, nusinersen-treated infants experienced fewer days of ventilation support ≥16 hours/day compared with sham procedure–treated infants by the end of the study (P=0.6091; Figure 11).

Figure 11. ENDEAR: Number of days requiring ventilation support ≥16 hours/day at the end of the study[a]



Abbreviations: CI, confidence interval; LSM, least squares mean
[a]Among all infants randomised who received ≥1 dose of nusinersen or sham procedure
[b]Based on analysis of covariance adjusting for each infant's disease duration and age at screening
[c]Difference of nusinersen – sham procedure
Source: Parsons 2018(3)

In conclusion, the odds of requiring permanent ventilation or any ventilation were >3 times or >11 times less likely, respectively, for nusinersen- vs. sham procedure–treated infants in ENDEAR.

References

1. Castro D, Farrar M, Finkel R, Tulinius M, Krosschell K, Saito K, et al. Longer-term Assessment of the Safety and Efficacy of Nusinersen for the Treatment of Infantile-Onset Spinal Muscular Atrophy (SMA): An Interim Analysis of the SHINE Study. In: American Academy of Neurology. Los Angeles, CA; 2018.
2. Tulinius M, Bruno C, Deconinck N, Schara U, Finkel R, Bhan I, et al. Nusinersen Decreases the Incidence and Length of Hospitalisations in Infants With Spinal Muscular Atrophy: Results From the ENDEAR Study. In: SMA Europe's International Scientific Congress on SMA. Krakow, Poland; 2018.
3. Parsons J, Ryan M, Finanger E, Zhang Y, Bhan I, Farwell W. Nusinersen Treatment Reduces the Likelihood of Requiring Ventilation Support in Infants With Spinal Muscular Atrophy: Results of the ENDEAR Trial. In: Muscular Dystrophy Association Clinical Conference. Arlington; 2018.
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Supplementary Appendix 2:

Cost-effectiveness model revisions and updated results

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Nusinersen (SPINRAZA®) for the treatment of 5q Spinal Muscular Atrophy

1.1 Background

This document sets out revisions to the cost-effectiveness model for nusinersen following the NICE appraisal consultation document (ACD). It provides descriptions of the introduced model changes, validation exercise and updated cost-effectiveness results presented with and without Biogen's commercial offer.

For version control the updated were applied to:

- ***Original version*** - Nusinersen (Spinraza)_NICE_CEM_Infantile and Later Onset_Final CIC_06 April 2018
- ***Revised version*** (in accompaniment to this appendix) - Nusinersen (Spinraza)_NICE_CEM_Early and Later Onset_Final CIC_ACD comments Final_

1.2 Revised model structure

[redacted], the revised model tracks 7 different groups of patients (Table 1). Patients with and without scoliosis surgery are tracked independently. Also, we track separately patients who are on the treatment and keep improving, those who are on the treatment and plateau, and those who discontinue treatment due to worsening or due to scoliosis. The original version did not track improving and worsening patients separately, instead the respective transition matrices (improvement, worsening, plateau) were applied to patient proportions within each health state.

Table 1 - Patient subgroups in the nusinersen Markov sheets

Patient subgroups		Progression
Patient with scoliosis surgery	1. Still on treatment (no plateau; i.e. keep improving)	Patients remain on treatment. We apply the nusinersen transition matrix were patients can remain on the same health state or move to the next best health state (Appendix Table 28 and Table 29).
	2. Still on treatment (plateau; i.e. remain in health state)	Patients remain on treatment. We apply a transition matrix were patients remain on the same health state (Appendix Table 30).
	3. Worsen (discontinue)	Patients discontinue treatment. The user can select between applying the RWC transition matrix or a transition matrix were 100% of patients transition to the next worst health state (Appendix Table 31 to Table 33).
	4. Discontinue due to scoliosis surgery	Patients discontinue treatment. The user can select between applying the RWC transition matrix or a transition matrix were 100% of patients transition to the next worst health state(Appendix Table 31 to Table 33).
Patients without scoliosis surgery	5. Still on treatment (no plateau)	Patients remain on treatment. We apply the nusinersen transition matrix were patients can remain on the same health state or move to the next best health state (Appendix Table 28 and Table 29).
	6. Still on treatment (plateau)	Patients remain on treatment. We apply a transition matrix were patients remain on the same health state (Appendix Table 30)
	7. Worsen (discontinue)	Patients discontinue treatment. The user can select between applying the RWC transition matrix or a transition matrix were 100% of patients transition to the next worst health state (Appendix Table 31to Table 33).

The diagram in Figure 1 shows the flow of patients in the nusinersen Markov sheets.

Each group of patients is estimated in the Markov nusinersen sheets based on three set of columns:

1. one set of columns estimates the number of patients entering the group (Group 1 HQ:HX; Group 2: EQ:QX, JW:KD, NQ:NX; Group 3 KF:KM, NZ:OG; Group 4 EZ:FG, HZ:IG; Group 5 AN:AU; Group 6 BG:BN; Group 7 BP:BW).

2. one set of columns apply the mortality adjustment for patients in that group (Group 1 II:IQ; Group 2 FI:FQ, KO:KW, OI:OQ; Group 3 KY:LG, OS:PA; Group 4 FS:GA, IS:JA; Group 5 AW:BE; Group 6 BY:CG; Group 7 CI:CQ)

3. one set of columns (colour coded) determine the health state membership of the mortality adjusted patients according to the corresponding transition matrix. (Group 1 JC:JK; Group 2 GC:GK, LI:LQ, PC:PK; Group 3 MC:MK, PW:QE; Group 4 GW:HE, MW:NE; Group 5 AD:AL; Group 6 CS:DA; Group 7 DM:DU)

This approach follows the same approach used by the ERG, where the mortality adjustment was performed in a separate group of columns in their own rebuild (please see section 1.3, validation).

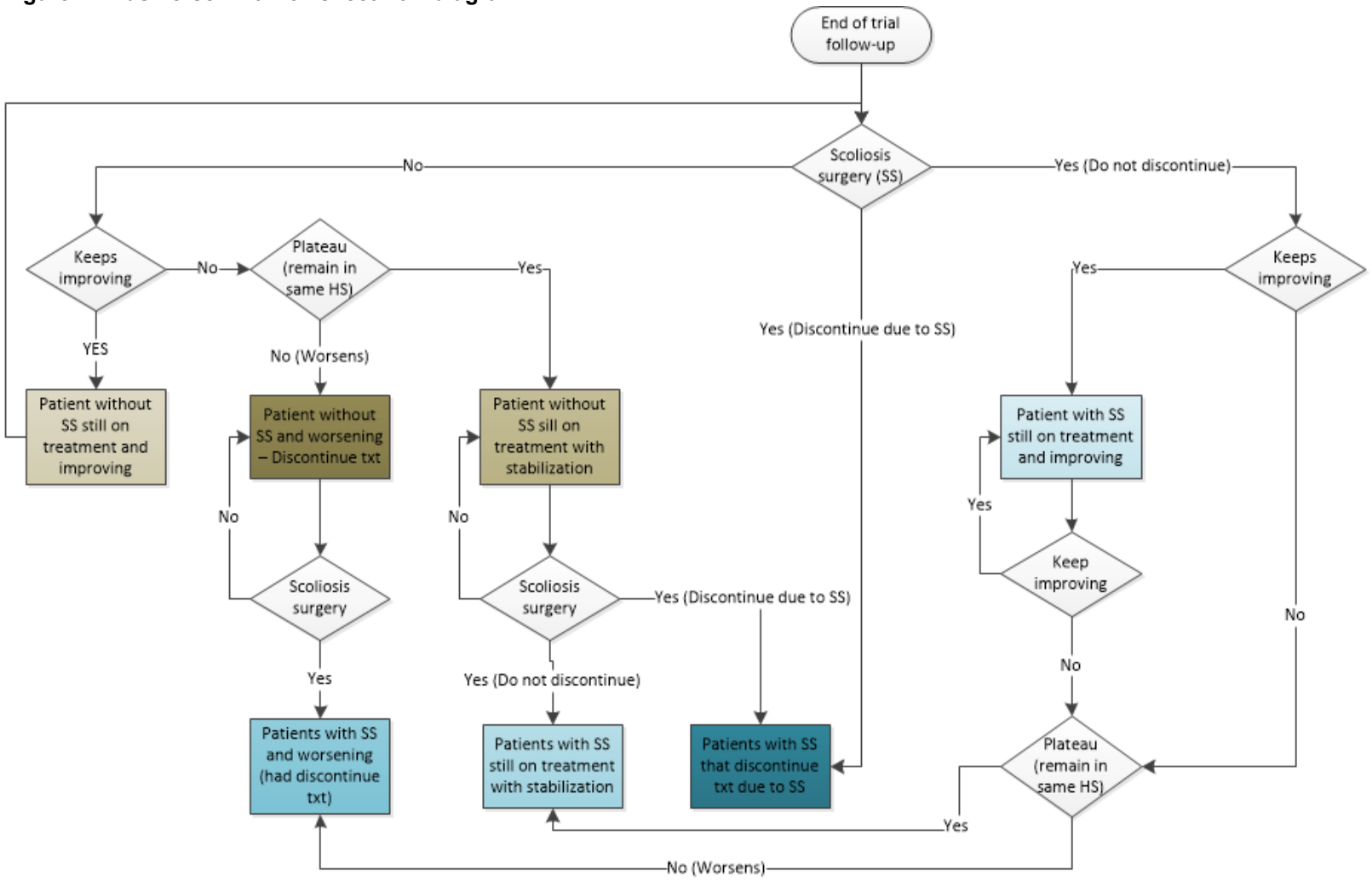
Other adjustments included in the revised model are:

- The option to select between two different transition matrices applied to those patients worsening ('Efficacy T1'!I135 = 2; 'Efficacy T2'!I115). In the original version, patients that worsen were assumed to follow the transition matrix for patients in the usual care (or real word care i.e. no treatment) arm. In the revised version, patients worsening can follow either the transition matrix used for the usual care arm or a transition matrix where 100% of patients worsening lose a milestone each cycle.

[redacted]

Additional revisions to the base case assumptions and settings are outlined in section 1.5.

Figure 1 - Nusinersen Markov sheet flow diagram



HS, Health state; SS, scoliosis surgery; txt, treatment

1.3 Validation exercise

1.3.1 Markov trace replication

The outcomes of the revised model were compared with the outcomes of the original model to validate the updated Markov traces. In the revised model, different patient groups are tracked separately. At each cycle, we estimated the proportion of patients on the treatment and who continue to improve, the proportion of patients that reach an improvement plateau and remain on the treatment, the proportion of patients that discontinue due to scoliosis surgery and due those discontinuing due to worsening (on the respective scales e.g. CHOP-INTEND, HFSME). We then applied one of the transition matrices available to each proportion of patients (nusinersen transition matrix [i.e. remain on the same health state or improve]; usual care transition matrix [remain on the same health state or worsen], plateau transition matrix [weighted average of plateau transition matrix and the worsen transition matrix]). In the original model, patients were not tracked separately, therefore we were unable to differentiate between patients worsening and patients improving; meaning that patients that worsened in a previous cycle could improve in the following cycle.

In the revised model we track separately the group of patients improving and the group of patients discontinuing nusinersen for three reasons: worsening, scoliosis surgery (impeding administration of further nusinersen doses) or death. The main assumption in the revised version is that once a patient enters the worsening or the scoliosis treatment discontinuation group, that patient will never regain milestones. Hence, when the both models (original and revised) are set to include patients that discontinue treatment due to scoliosis surgery (i.e. 'Efficacy T1'!I55 > 0%; 'Efficacy T2'!I39 > 0%) or patients that worsen ('Efficacy T1'!B111 = Yes AND 'Efficacy T1'!I127:I132 > 0%; 'Efficacy T2'!B93 = Yes AND 'Efficacy T1'!I108:I112 > 0%), the results and nusinersen Markov traces are different in both models. The impact of discontinuation due to scoliosis or worsening in the revised model are assessed in following sub sections.

For the purpose of this validation exercise, when discontinuation due to scoliosis surgery is set to 0% and 0% of patients are assumed to worsen, the revised and original produce the same results (Table 2 - Early onset results and Table 3 - Later onset results; using treatment dependent baseline distributions as per the original model). The models produce the same results as the ERG's model rebuild (under the same settings of no treatment discontinuation due to scoliosis surgery and no worsening).

The results presented below were run using the list price of £75,000 per vial.

Table 2 - Early onset results – 0% of patients have scoliosis and 0% of patients worsen

Early Onset	Incr. Costs	Incr. QALYs (Patients)	ICER (Patients)
Original	2,201,891	5.37	409,837
Revised	2,201,891	5.37	409,837

Table 3 - Later onset results – 0% of patients have scoliosis and 0% of patients worsen

Later Onset	Incr. Costs	Incr. QALYs (Patients)	ICER (Patients)
Original	3,230,579	2.40	1,344,681
Revised	3,230,579	2.40	1,344,681

Additional scenarios were conducted to assess the impact of model updates between the original and the revised model were performed. Scenarios include:

- Discontinuation due to scoliosis surgery
- Discontinuation due to worsening (milestones)

1.3.2 Treatment discontinuation following scoliosis surgery

In the original version, we estimated the proportion of patients who discontinued due to scoliosis surgery in each cycle and applied the usual care transition matrix to this proportion of patients in each health state which results in the trace observed in Figure 2. In essence, as these patients were not tracked separately, a patient could worsen in one cycle and subsequently improve in the next. In the revised model patients discontinuing nusinersen due to scoliosis surgery are tracked separately and keep worsening, never regaining milestones.

Results when the treatment discontinuation due to scoliosis surgery is set to 20% ('Efficacy T1'!I55; 'Efficacy T2'!I39) are presented in Table 4 with Markov traces shown on

Figure 2 and Figure 3 for early onset SMA. As the assumed proportion of early onset patients receiving scoliosis surgery in the original model was low (1% in each arm, see section 1.5 for revisions), this coupled with the high mortality rates and therefore the low proportion of patients who reach 12-15 years of age (after which patient have scoliosis surgery in the model), leads to a negligible impact on model outcomes.

The results presented below were run using the list price of £75,000 per vial.

Table 4 - Early onset – discontinuing due to scoliosis surgery

Early Onset	Incr. Costs	Incr. QALYs (Patients)	ICER (Patients)
Original	2,201,891	5.3726	409,837
Revised	2,201,891	5.3716	409,917

Figure 2 - Markov trace nusinersen original model – early onset, discontinuing due to scoliosis surgery

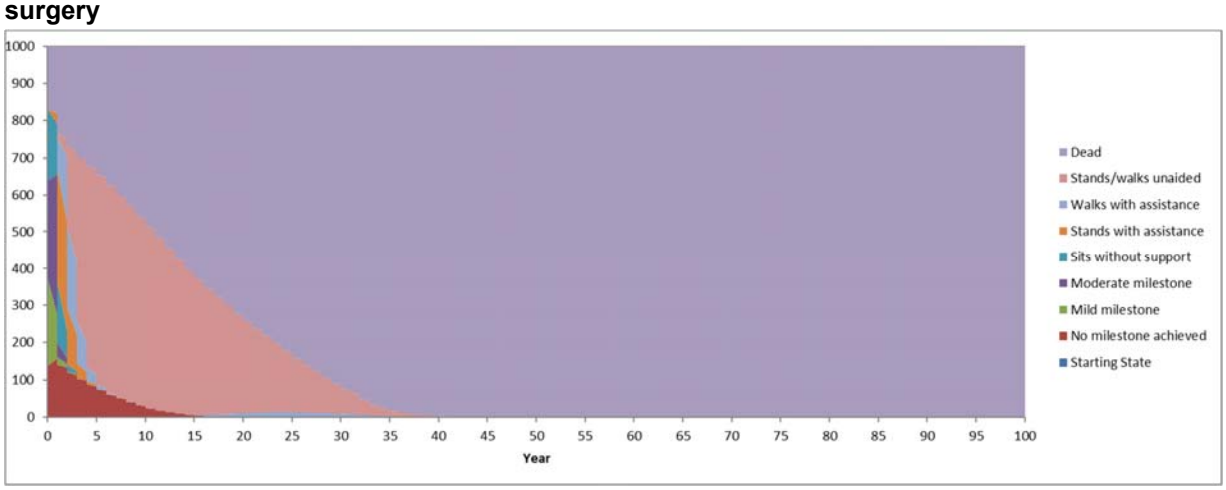
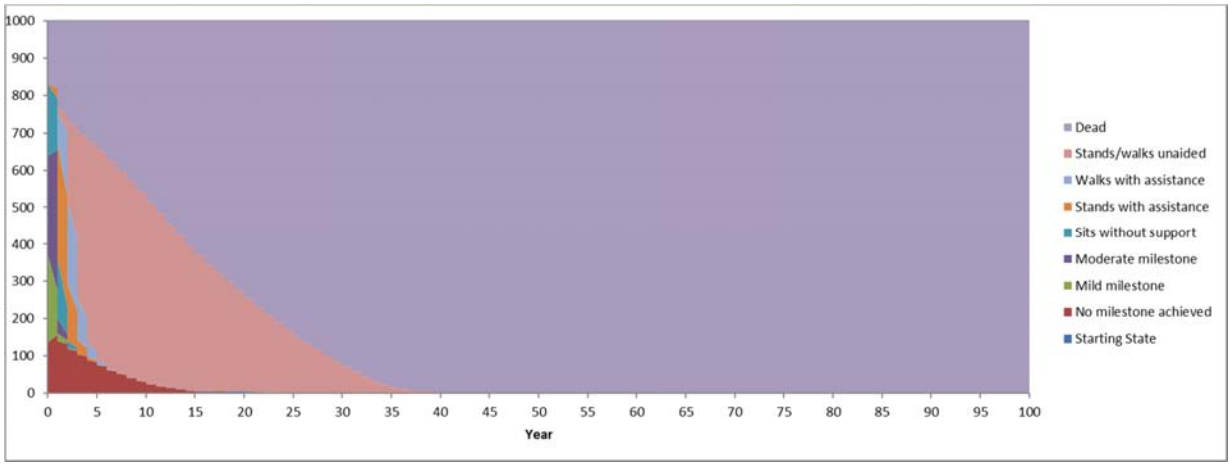


Figure 3 - Markov trace nusinersen revised model – early onset, discontinuing due to scoliosis surgery



Results for the later onset model are presented in Table 5 with the respective Markov traces in Figure 4 and Figure 5. The impact of scoliosis is greater in the later onset model given the proportion of patients reaching 12 (non-ambulant) and 15 (ambulant) years of age respectively. In the revised model the 20% of patients who discontinue following surgery never regain milestones, hence the reduced incremental QALY gains and increased ICER.

Table 5 - Later onset results – discontinuing due to scoliosis surgery

Later Onset	Incr. Costs	Incr. QALYs (Patients)	ICER (Patients)
Original	2,964,442	2.37	1,252,991
Revised	2,968,984	2.24	1,325,758

Figure 4 - Markov trace nusinersen original model – later onset, discontinuing due to scoliosis surgery

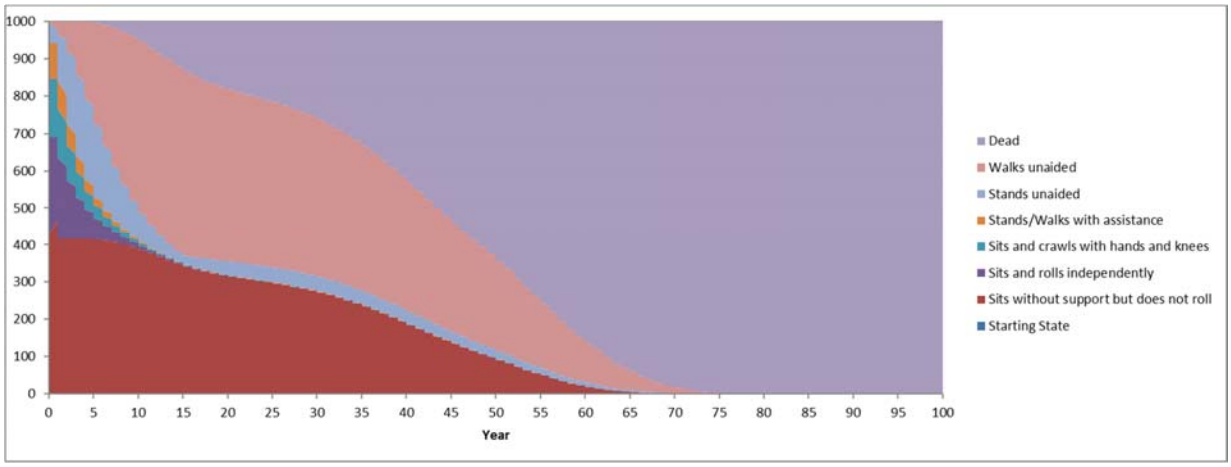
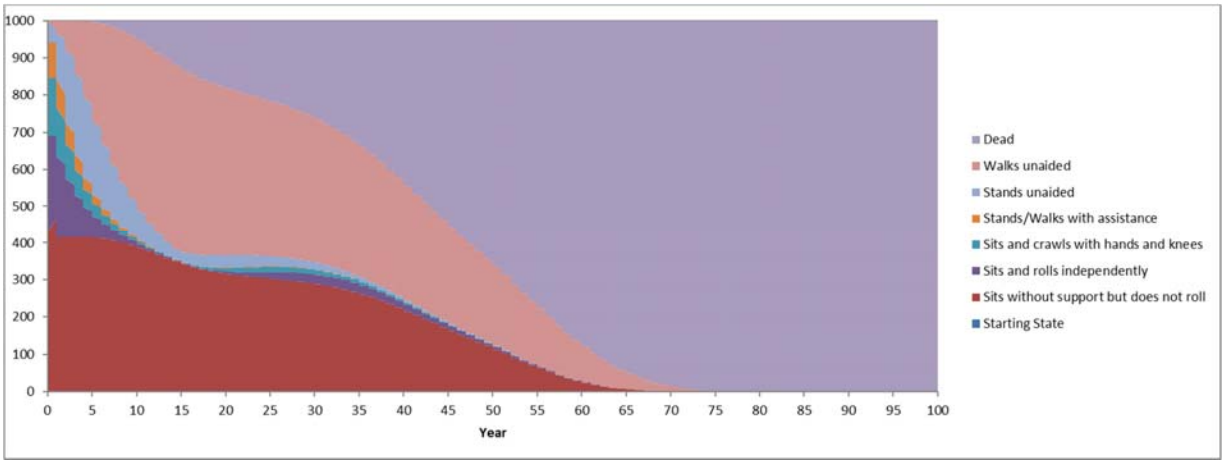


Figure 5. Markov trace nusinersen revised model – later onset, discontinuing due to scoliosis



1.3.3 Discontinuation due to worsening

NB. To enter a proportion of patients worsening post trial follow-up, the dropdowns in the revised model 'Efficacy T1'!B111 and 'Efficacy T2'!B93 need to be set to “Yes”.

In the original version , the assumption that 5% of patients reach an improvement plateau ('Efficacy T1'!I126:I132; 'Efficacy T2'!I107:I112; Figure 6 and Figure 8) and that 100% of those patients reaching an improvement plateau (original version: 'Efficacy T1'!I135, 'Efficacy T2'!I115; revised version: 'Efficacy T1'!I136, 'Efficacy T2'!I116) worsen using the usual care transition matrix (fixed to the usual care transition matrix in the original version; revised version: 'Efficacy T1'!I135 = 2; 'Efficacy T2'!I115 = 2) produce the trace shown in Figure 7 and Figure 9 for early and later onset, respectively.

In the revised model, as patients worsening do not regain milestones, the proportion of patients need to be reduced to produce a similar trace to reflect the original version. For example, applying a 5% in the revised version ('Efficacy T1'!I126:I132; 'Efficacy T2'!I107:I112; Figure 12 and Figure 14) implies that 5% of the patients that have not yet stop improving will discontinue at each cycle, producing a trace which is not representative of the assumption in the original version where an overall 5% is applied to all patients (not just those still improving; Figure 13 and Figure 15). When the percentage of patients reaching the improvement plateau (out of which 100% worsen using the usual care transition matrix) is set to 1% in the revised early onset model and to 0.5% in the revised later onset model (Figure 10 and Figure 16), the resulting traces are closer to the ones observed in the original version (Figure 11 and Figure 17).

Table 6. Early onset - Patients worsening

Early Onset	Incr. Costs	Incr. QALYs (Patients)	ICER (Patients)
Original	2,087,849	5.18	403,123
Revised (5% worsening per cycle)	1,090,905	2.64	413,837
Revised (1% worsening per cycle)	1,792,069	4.36	410,914

Figure 6. Worsening inputs Previous model – Early Onset

Assume that a proportion of patients still on treatment reach a plateau and stop improving?

YES

	User	Default
Month after which a proportion of patients still on treatment stop improving and remain in the same health state		
No milestones achieved	13	24
Mild milestones	13	24
Moderate milestones	13	24
Sits without support	13	36
Stands with assistance	13	36
Walks with assistance	13	36
Stands/Walks unaided	13	60
% patients still on treatment who stop improving (remain on the same health state)		
No milestones achieved	5%	50%
Mild milestones	5%	50%
Moderate milestones	5%	50%
Sits without support	5%	100%
Stands with assistance	5%	100%
Walks with assistance	5%	50%
Stands/Walks unaided	5%	10%
% of patients of those reaching an improvement plateau which start getting worse	100%	0%

(i.e. 100% of those patients reaching an improvement plateau progress as in the RWC arm

Figure 7. Markov trace nusinersen original model – Early onset, patients worsening

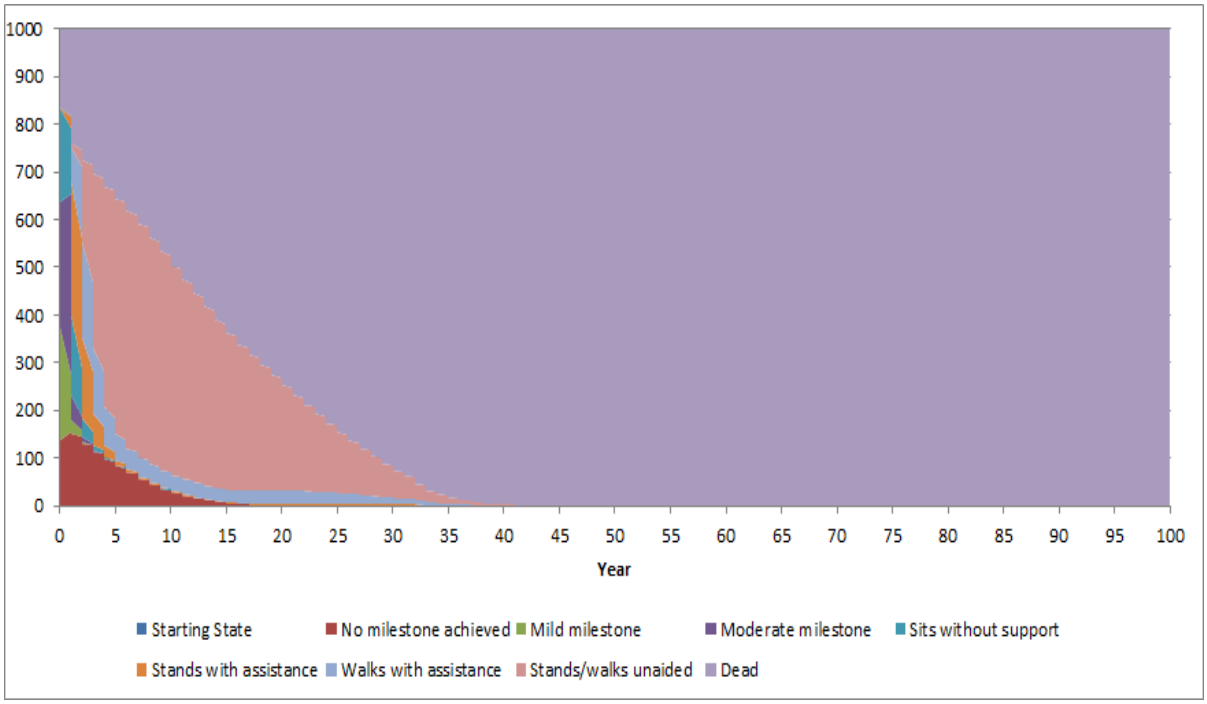


Figure 8. Worsening inputs Revised model – Early onset

Assume that a proportion of patients still on treatment reach a plateau and stop improving?

YES

	User	Default
Month after which a proportion of patients still on treatment stop improving and remain in the same health state		
No milestones achieved	13	13
Mild milestones	13	13
Moderate milestones	13	13
Sits without support	13	13
Stands with assistance	13	13
Walks with assistance	13	13
Stands/Walks unaided	13	13
% patients still on treatment who stop improving (remain on the same health state or worsen)		
No milestones achieved	100%	100%
Mild milestones	5.0%	5%
Moderate milestones	5.0%	5%
Sits without support	5.0%	5%
Stands with assistance	5.0%	5%
Walks with assistance	5.0%	5%
Stands/Walks unaided	5.0%	5%
To those patients plateauing: Enter 1 to assume 100% worsen to the next worst health state / 2 to apply the RWC transition matrix	2	2
% of patients of those reaching an improvement plateau which start getting worse	100%	100%

(i.e. 100% of those patients reaching an improvement plateau progress as in the RWC arm)

Figure 9. Markov Trace Nusinersen Revised Model – Early Onset, 5% Patients worsening

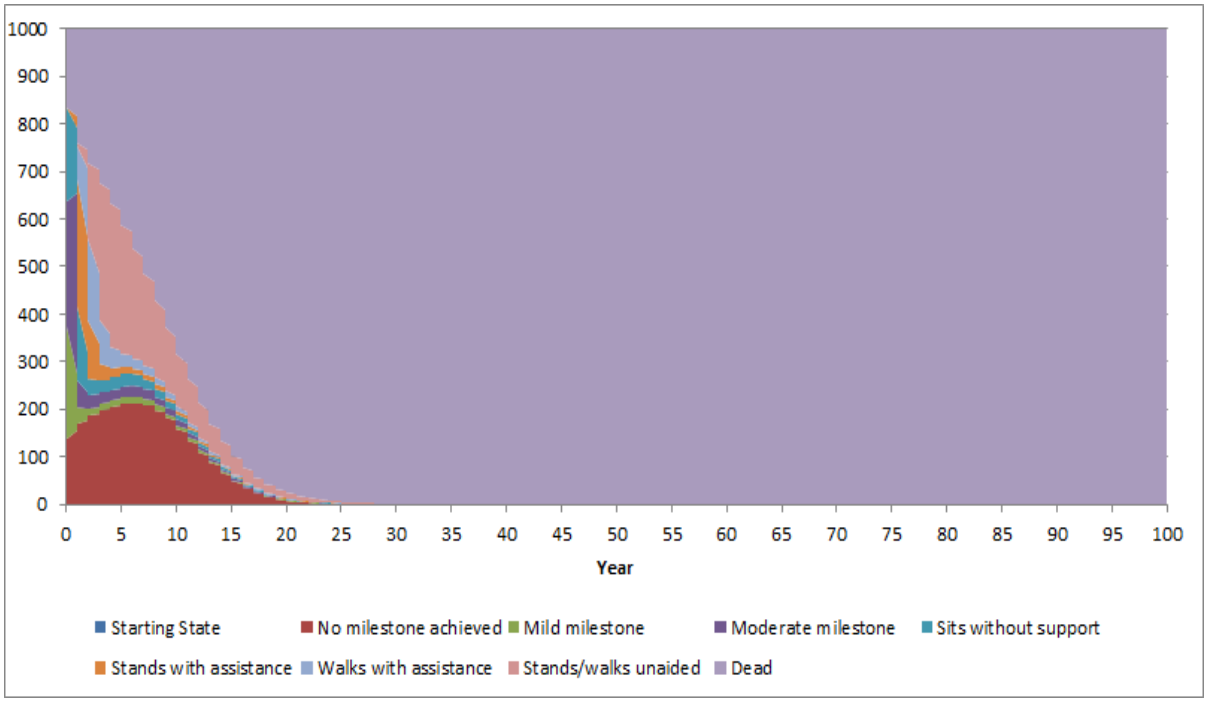


Figure 10. Worsening inputs revised model – early onset, 1% patients worsening per cycle

Assume that a proportion of patients still on treatment reach a plateau and stop improving?

YES

	User	Default
Month after which a proportion of patients still on treatment reach an improvement plateau and stay in current health state		
Sits without support but does not roll	15	15
Sits and rolls independently	15	15
Sits and crawls with hands and knees	15	15
Stands/Walks with assistance	15	15
Stands unaided	15	15
Walks unaided	15	15
% patients still on treatment who stop improving (remain on the same health state or worsen)		
Sits without support but does not roll	100%	100%
Sits and rolls independently	1%	1%
Sits and crawls with hands and knees	1%	1%
Stands/Walks with assistance	1%	1%
Stands unaided	1%	1%
Walks unaided	1%	1%
To those patients plateauing: Enter 1 to assume 100% worsen to the next worst health state / 2 to apply the RWC transition matrix	2	2
% of patients of those reaching an improvement plateau which start getting worse	100%	100%

(i.e.100% of those patients reaching an improvement plateau progress as in the RWC arm)

Figure 11. Markov trace nusinersen revised model – early Onset, 1% patients worsening per cycle

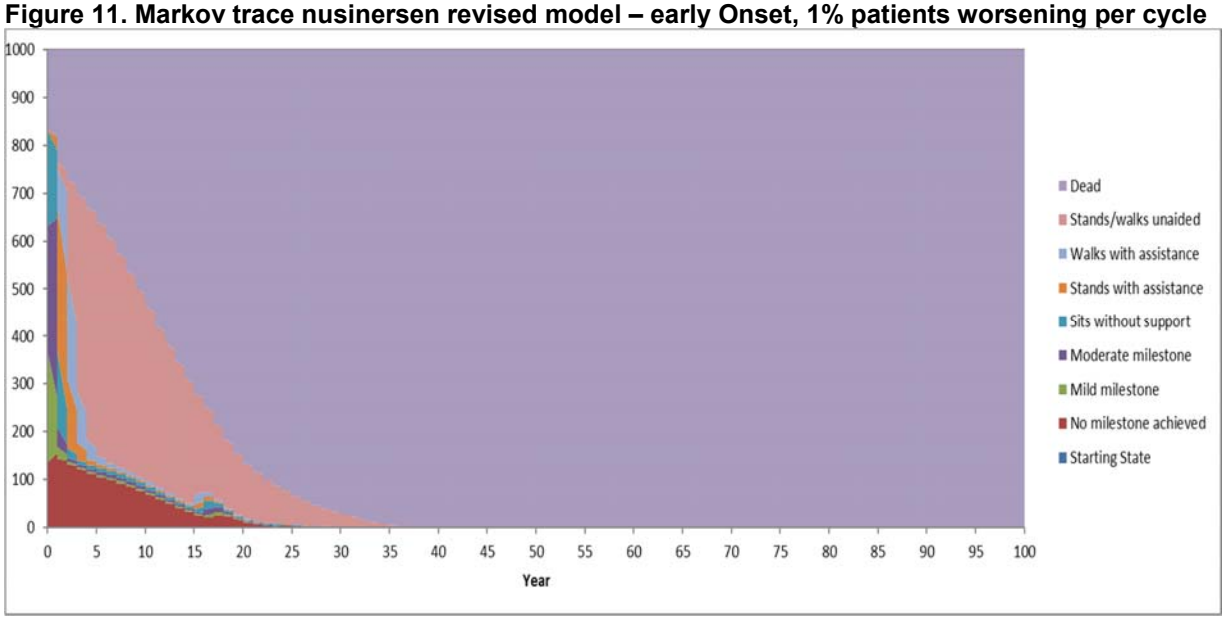


Table 7. Later onset - Patients worsening

Later Onset	Incr. Costs	Incr. QALYs (Patients)	ICER (Patients)
Original	2,937,104	2.30	1,274,636
Revised (5% worsening per cycle)	1,159,078	0.78	1,485,199
Revised (0.5% worsening per cycle)	2,476,915	1.89	1,310,746

Figure 12. Worsening inputs original model – later onset overall 5% of patients worsening

Assume that a proportion of patients still on treatment reach a plateau and stop improving?

YES

	User	Default
Month after which a proportion of patients still on treatment reach an improvement plateau and stay in current health state		
Sits without support but does not roll	15	36
Sits and rolls independently	15	36
Sits and crawls with hands and knees	15	36
Stands/Walks with assistance	15	36
Stands unaided	15	60
Walks unaided	15	60
% patients still on treatment reaching improvement plateau (remain on the same health state)		
Sits without support but does not roll	5%	50%
Sits and rolls independently	5%	50%
Sits and crawls with hands and knees	5%	50%
Stands/Walks with assistance	5%	50%
Stands unaided	5%	50%
Walks unaided	5%	10%
% of patients of those reaching an improvement plateau which start getting worse	100%	0%

(i.e.100% of those patients reaching an improvement plateau progress as in the RWC arm

Figure 13. Markov trace nusinersen original model – later onset, 5% patients worsening overall

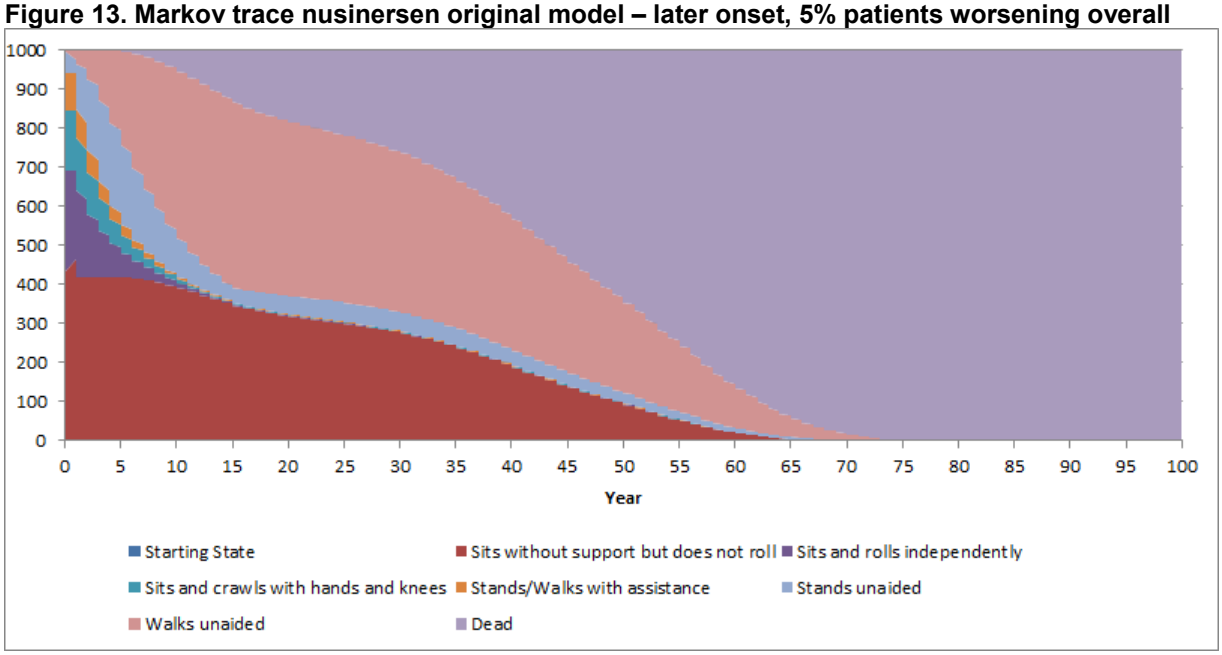


Figure 14. Worsening inputs Revised model – later onset, 5% patients worsening

Assume that a proportion of patients still on treatment reach a plateau and stop improving?

YES

	User	Default
Month after which a proportion of patients still on treatment reach an improvement plateau and stay in current health state		
Sits without support but does not roll	15	15
Sits and rolls independently	15	15
Sits and crawls with hands and knees	15	15
Stands/Walks with assistance	15	15
Stands unaided	15	15
Walks unaided	15	15
% patients still on treatment who stop improving (remain on the same health state or worsen)		
Sits without support but does not roll	100%	100%
Sits and rolls independently	5%	5%
Sits and crawls with hands and knees	5%	5%
Stands/Walks with assistance	5%	5%
Stands unaided	5%	5%
Walks unaided	5%	5%
To those patients plateauing: Enter 1 to assume 100% worsen to the next worst health state / 2 to apply the RWC transition matrix	2	2
% of patients of those reaching an improvement plateau which start getting worse	100%	100%

(i.e.100% of those patients reaching an improvement plateau progress as in the RWC arm)

Figure 15. Markov Trace Nusinersen Revised Model – Later Onset, 5% Patients worsening

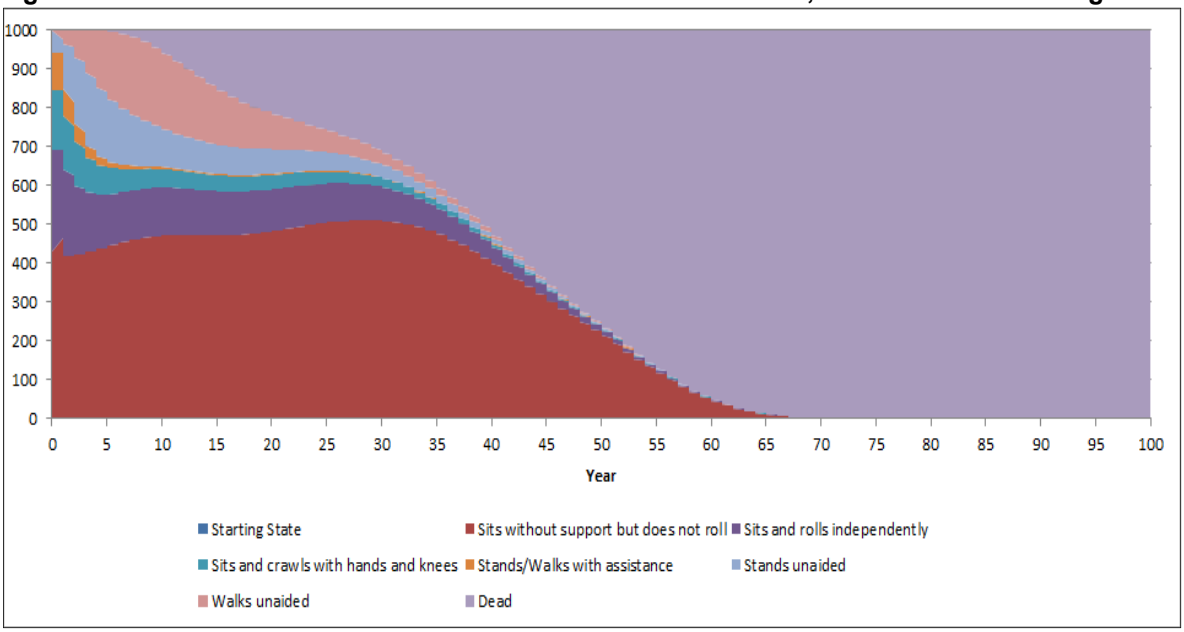


Figure 16. Worsening inputs Revised model – Later onset, 0.5% Patients worsening

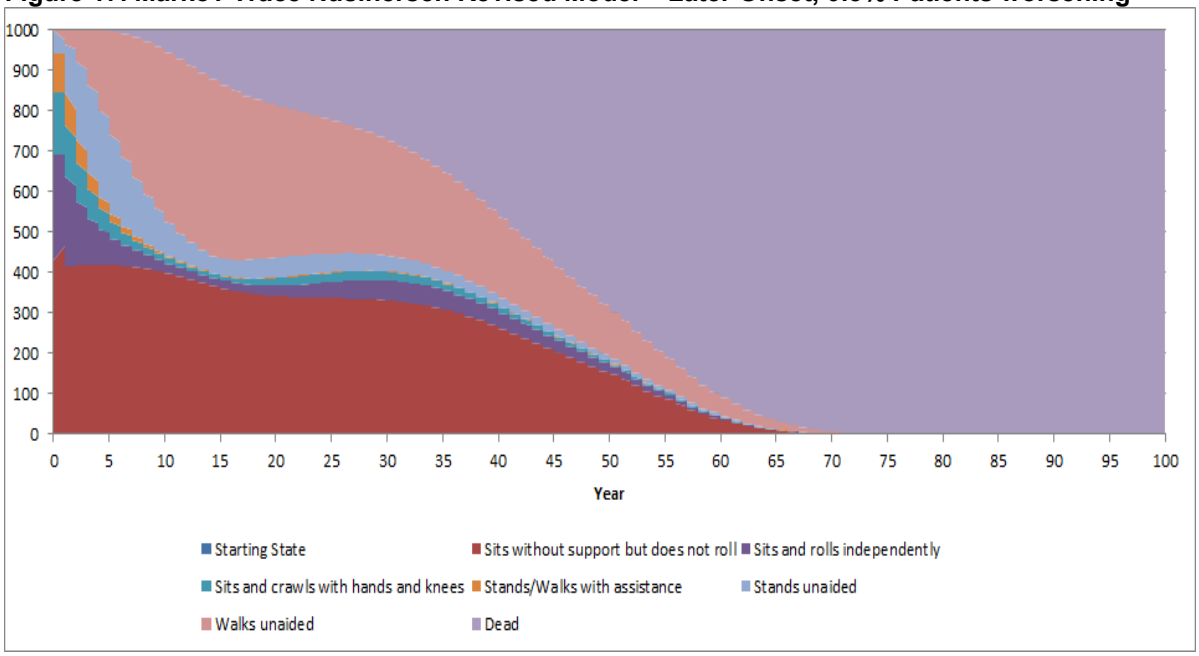
Assume that a proportion of patients still on treatment reach a plateau and stop improving?

YES

	User	Default
Month after which a proportion of patients still on treatment reach an improvement plateau and stay in current health state		
Sits without support but does not roll	15	15
Sits and rolls independently	15	15
Sits and crawls with hands and knees	15	15
Stands/Walks with assistance	15	15
Stands unaided	15	15
Walks unaided	15	15
% patients still on treatment who stop improving (remain on the same health state or worsen)		
Sits without support but does not roll	100%	100%
Sits and rolls independently	0.5%	5%
Sits and crawls with hands and knees	0.5%	5%
Stands/Walks with assistance	0.5%	5%
Stands unaided	0.5%	5%
Walks unaided	0.5%	5%
To those patients plateauing: Enter 1 to assume 100% worsen to the next worst health state / 2 to apply the RWC transition matrix	2	2
% of patients of those reaching an improvement plateau which start getting worse	100%	100%

(i.e.100% of those patients reaching an improvement plateau progress as in the RWC arm)

Figure 17. Markov Trace Nusinersen Revised Model – Later Onset, 0.5% Patients worsening



[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.5 Revised base case & scenario assumptions

Biogen have revised base case assumptions within the revised model in light of the ERG report and ACD commentary, including:

- Assumptions regarding the expected trajectory of nusinersen-treated patients through modelled motor milestone health states;
- Assumptions regarding the expected survival of nusinersen-treated patients;
- Estimated patient utilities;
- Estimated caregiver disutilities;
- Estimated health state costs.

All changes are made in isolation with other assumptions aligned with those in the original model/company submission but implemented in the revised model structure. All analyses are run at a list price of £75,000 per vial. In section 1.7, all revisions are implemented together using the revised model at the list price and commercial with a series of scenario analyses

1.5.1 Transition probabilities

The ACD document notes that the long-term transition probabilities whereby nusinersen could not get worse but patients treated with 'usual care' (or 'best supportive care') could not improve, was not consistent with trial data, in which a small proportion of patients on sham therapy had improvements in symptoms over almost all time periods. The clinical experts noted that without treatment with nusinersen it was plausible that 5q spinal muscular atrophy (SMA) would progressively worsen with no observable improvement. Therefore, Biogen have made no changes to usual care trajectory post-trial follow-up in the models (i.e. patients cannot improve beyond trial follow-up) but have provided scenarios analyses (section 1.7) assessing slower rates of monthly decline from the existing literature (Table 8).

Table 8. Mean monthly decline in CHOP-INTEND (early onset) and HFMSE (later onset)

Mean monthly decline	Base Case (trial data)	Scenario
Early onset (CHOP-INTEND)	[redacted]	0.11(1)
Later onset (HFMSE)	[redacted]	0.05(2)

The clinical experts considered it implausible that SMA treated with nusinersen could not get worse and this did not represent clinical practice where a distribution across improvement and worsening would likely be observed. The committee favoured the ERG's exploratory analyses in which an overall 5-10% of patients worsen were more suitable for decision making. As the revised model separately tracks patients worsening, implementing 5-10% per cycle would overestimate this proportion versus the original model (as shown in the validation section).

It should be acknowledged that within original the early onset model, all patients in the *'no milestones'* health state at the end of ENDEAR (month 13) are assumed to discontinue treatment and follow the trajectory of the usual care group i.e. only patients demonstrating improvement were assumed to remain on therapy and continue to improve. Similarly, in the later onset model, all patients in the *'sits without support but does not roll'* at the end of CHERISH (month 15) are assumed to discontinue treatment and follow the trajectory of the usual care arm.

Post-trial follow-up, aside from scoliosis, functionality was incorporated into both original economic models to allow a specified proportion of patients to reach an improvement plateau post month 13/15 and either remain in the same health state (plateau) or follow the trajectory of the usual care arm. There is currently no evidence of treatment discontinuation (with the exception of death) from the clinical trials.

[redacted]

In light of this, there is also no evidence to suggest whether patients who reach an improvement plateau, or do not benefit from nusinersen in the longer term, follow a disease trajectory faster, the same or slower than usual care group.

Biogen have further revised both early and later onset models to accommodate the preferred committee assumptions including an option whereby a proportion of patients lose a milestone per cycle. In the base case this is assumed at 1% of patients who discontinue due to worsening per cycle and follow the usual care transition matrix. In scenario analyses, an increased percentage of 2% per cycle in addition to alternative trajectories (i.e. 1% patients per cycle losing 1 milestone per cycle) are assessed.

Furthermore, the ERG expressed concern regarding the treatment dependent nature of health state thresholds based on CHOP-INTEND and HFMSE in the original early and later onset models, respectively. Under this assumption a patient would require different score thresholds to be classified in a particular health state dependent upon the treatment arm. In the revised model Biogen has updated this setting so that health state thresholds are based on the ITT population with both arms combined for all analyses (i.e. treatment independent). Impact of the revised assumption is presented in Table 9 and Table 10. In both scenarios incremental costs and QALYs are reduced and ICERs increase.

The results presented below were run using the list price of £75,000 per vial and assumptions from the original model/ submission.

Table 9. Early onset model results

Early Onset	Incr. Costs	Incr. QALYs (Patients)	ICER (Patients)
Original assumption (ITT each arm)	2,189,113	5.34	409,981
Revised assumption (ITT both arms combined)	2,176,880	5.29	411,701

Table 10. Later onset model results

Later Onset	Incr. Costs	Incr. QALYs (Patients)	ICER (Patients)
Original assumption (ITT each arm)	2,968,464	2.24	1,325,526
Revised assumption (ITT both arms combined)	2,969,830	2.23	1,334,710

1.5.2 Survival extrapolations

The ACD notes that an overall survival gain with nusinersen in early onset SMA has been observed in clinical trials and heard that this gain has also been observed within clinical practice. Clinical experts noted that nusinersen may help preserve respiratory muscle function and therefore it would be reasonable to predict longer-term survival benefit. The ERG deemed the approach to extrapolation in the early onset model to be overly complex and highly optimistic given the 0.9 mortality adjustment applied to the best health states to represent a mortality risk similar to that for patients with less severe SMA.

The ERG also had concerns around the use of Gregoretti et al. (2013) continuous non-invasive respiratory muscle aid (NRA) data to represent the usual care arm, and the ERG considered that a simpler approach based on extrapolating parametric models fitted to observed trial data may have been both more informative and more transparent than the approach adopted in the original submission. In the revised model, Biogen have accepted the ERG critique and have updated the base case settings for early onset SMA (please note all changes were available for selection in the original model). As no survival benefit was observed in CHERISH for later onset SMA, no changes have been made to survival estimates with the exception of removing the mortality adjustment (not applied or '0' in the base case) with an alternative mortality adjustment (0.5) assessed in scenario analyses.

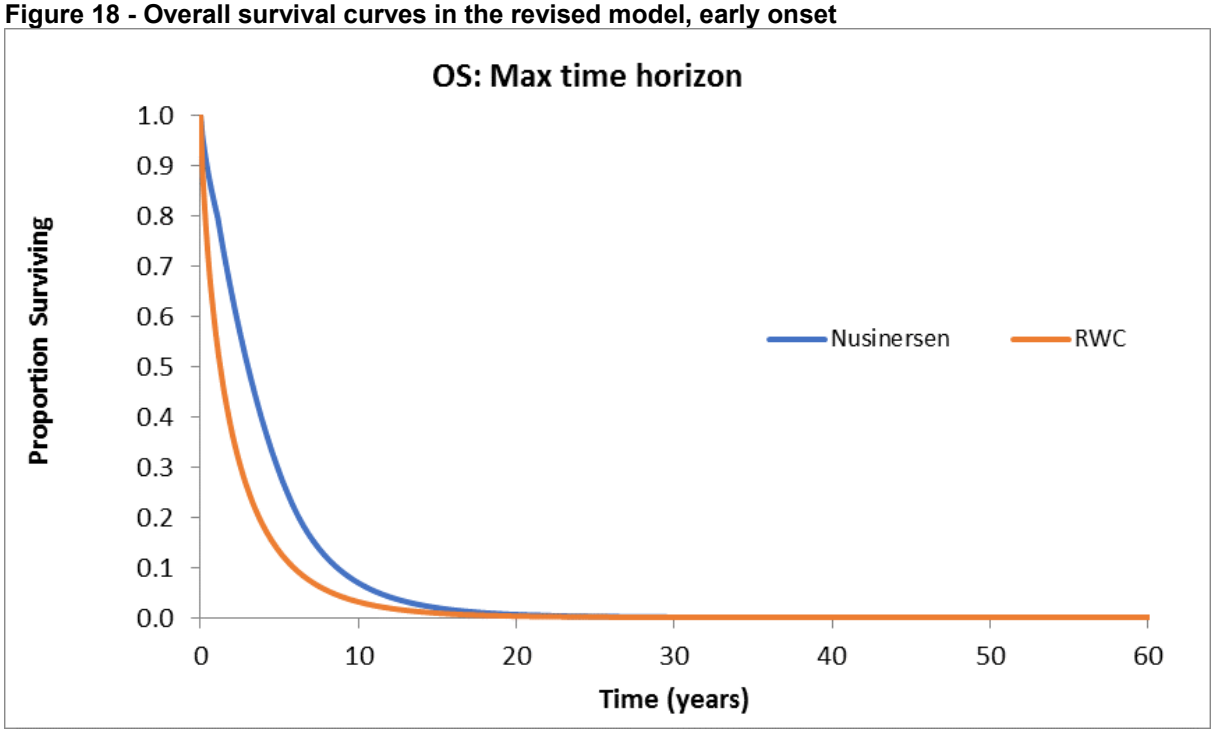
For the early onset model a Weibull survival function was fitted to the observed Kaplan-Meier curves for the study arms of the ENDEAR trial. As mentioned in the response to the ERG comments, the models that produce plausible long-term survival predictions (Weibull) do not fit the data well (Figure 30, Figure 31, Figure 32, Figure 33 Appendix – original submission). Of the options included in the model, the Weibull function was the only survival function that predicted a plausible long-term extrapolation for patients in the RWC arm. Other functions (which fitted the data well) predicted unrealistic long-term survival. Therefore, the Weibull function was selected as the base case when external long-term data is not used to guide survival extrapolation after trial follow-up. A more conservative approach was taken in modelling nusinersen-treated patients in the better health states with mortality adjustment not applied in the base case (assessed in scenario analyses). Instead, the within trial hazard ratio (HR) was tapered over a period of 60 months. Both of these assumptions have been explored further in scenario analyses.

Table 11 presents the impact of all above listed changes on observed model outcomes (excluding worsening in both sets of results). The updated survival curve is presented in Figure 18). In both arms in the revised model, survival estimates are reduced compared to the original model in the absence of the external data and further with nusinersen due to the mortality adjustment factor not applied; undiscounted life years decrease from 3.87 to 2.32 and 13.01 to 4.02 in the usual care and nusinersen arms, respectively. The usual care arm, estimates are closer to the existing literature and that expected by UK clinicians with estimates of 2 years. In the absence of long-term data, it is unknown where the true estimate for nusinersen lies.

Table 11. Early onset model outcomes

	Submission settings		Revised settings	
	Nusinersen	**Usual Care**	**Nusinersen**	**Usual Care**
Outcomes (% of patients over analysis time frame) by health state				
Max % of patients ever achieving later onset (Type II) motor milestones	55.2%	2.6%	46.9%	3.3%
Max % of patients ever achieving later onset (Type III) motor milestones	56.8%	0.0%	25.8%	0.0%
Mean time on treatment with Nusinersen (years)	12.01	0	3.57	0
Overall survival (LY) (undiscounted)	13.01	3.87	4.02	2.32
Overall survival (LY) (discounted)	9.34	3.39	3.59	2.12

Figure 18 - Overall survival curves in the revised model, early onset



1.5.3 Patient utilities

It is acknowledged within the ACD that the assessment of health related quality of life (HRQoL) is extremely difficult in children and young people(3,4). Conceptually, HRQoL for children, particularly infants, will depend on different factors from those important to adults. Practically, the difficulties of administering HRQoL questionnaires to infants and children necessitate the use of caregivers as proxies who may not be able to represent patients adequately. Generally, the assessment of HRQoL in children is not well developed; the Paediatric Quality of Life Inventory (PedsQL) measure is frequently used in spinal muscular atrophy (SMA), and there is some evidence for its validity, but reservations have been expressed about this instrument. There are no HRQoL measures available for use in infants.

Due to the difficulties of measuring HRQoL in children, no measures were included in the ENDEAR trial. The health states defined in the cost-effectiveness model are based on gross motor functions and may therefore neglect changes in fine motor functions which can be important to patients with SMA. Where treatment is expected to improve survival beyond the normal life expectancy of patients with SMA (particularly in early onset), there is no precedence on which to base HRQoL assessments. In addition, there are several clinical aspects that were not captured in the nusinersen clinical trials and therefore the impact on patients' HRQoL was excluded from the models; it is likely that the innovative benefits of nusinersen will help to mitigate at least some of these. In this way it is likely that the base case for the economic model represents a conservative estimation. These areas include:

- Swallowing, time it takes to feed child and make up feeds
- Speech and other forms of communication
- Weight over/under gain
- Aspiration frequency
- Cough and time required for chest physio and cough assist
- Pain
- Contracture management / contracture stretching
- Fracture frequency and management
- Joint dislocation
- Gut dysmotility and constipation
- Pressure sores and their management
- Psychological impact
- Impact on siblings and family
- Frequency of infections
- Scoliosis
- Broader lung function tests in older children

Furthermore, it should be noted that patients have normal intelligence and are fully aware of their fate and the limitations of current standard of care.(5) The associated fear of losing abilities and independence imposes a major psychological burden on patients and carers as consistently cited in numerous statements from the patient advisory group submissions.(6–8).

The measurement of utilities required to estimate quality-adjusted life years (QALYs) adds another layer of complexity. In the absence of directly assessed utilities (e.g. European Quality of Life-5 Dimensions [EQ-5D] questionnaire), indirect approaches are required. One mapping algorithm is available to convert PedsQL data into EQ-5D in SMA patients but it may not be generalisable specifically to SMA patients as noted by the ERG.(9) It is also assumed that the utility of any given health state is constant over time. In all, reducing a patient's life experience to a single number might not be appropriate for SMA – the EQ-5D scale may be insufficiently sensitive to capture all aspects of HRQoL. A more balanced cost consequences analysis could be more appropriate than a cost utility analysis.

A number of approaches to the estimation of health state utilities have been explored by Biogen and the ERG including the PedsQL mapped to EQ-5D, the case vignette and the clinical advisor estimations. It is noted that all of these options have serious limitations, but all would be considered in decision making. For the purpose of model revisions, values from the case vignette study have been used in the base case with the PedsQL and clinical advisor estimates assessed in scenario analyses (Table 12). The effect of using case vignettes in both models is presented in Table 13 and Table 14.

Table 12. - Health state utilities under different approaches

Health state	Case Vignettes	PedsQL mapped	ERG clinical advisers
Early Onset			
No Milestone Achieved	-0.240	[redacted]	0.200
Mild Milestones	-0.120	[redacted]	0.250
Moderate Milestones	-0.170	[redacted]	0.350
Sits Without Support	-0.040	[redacted]	0.600
Stands With Assistance	0.040	[redacted]	0.650
Walks With Assistance	0.520	[redacted]	0.750
Stands/Walks Unaided	0.710	[redacted]	0.850
Later Onset			
Sits Without Support But Does Not Roll	0.040	[redacted]	0.600
Sits and Rolls Independently	0.040	[redacted]	0.600
Sits and Crawls With Hands and Knees	0.100	[redacted]	0.600
Stands/Walks With Assistance	0.390	[redacted]	0.750
Stands Unaided	0.720	[redacted]	0.850
Walks Unaided	0.720	[redacted]	0.850

The results presented below were run using the list price of £75,000 per vial and all other assumptions from the original model.

Table 13. Early Onset – Case Vignettes

Early Onset	Incr. Costs	Incr. QALYs (Patients)	ICER (Patients)
Original assumption (mapped PedsQL)	2,189,113	5.34	409,981
Revised assumption (case vignette)	2,189,113	5.17	423,528

Table 14. Later Onset – Case Vignettes

Later Onset	Incr. Costs	Incr. QALYs (Patients)	ICER (Patients)
Original assumption (mapped PedsQL)	2,968,464	2.24	1,325,526
Revised assumption (case vignette)	2,968,464	6.62	448,452

1.5.4 Caregiver utilities

Carer impacts are not explicitly part of the NICE reference case but can be taken into account where they are considered to be important. However, the methodology for assessing caregivers' quality of life is not well developed.

Like other orphan diseases, there is little quantitative evidence about the impact of SMA on caregivers' HRQoL or other important facets of their lives. However, for SMA there is now substantial qualitative evidence on the impact on caregivers.

A high proportion of working parents of patients with SMA have to reduce their hours or even leave their jobs, leading to financial strain and further impacting on their HRQoL(10). A survey of SMA families in Scotland (n=19; n=2 with type I or II, n=17 with type II or III) found that 79% (n=15/19) of the main unpaid carers had to give up work completely or drop to part time.(11) Parents of children with SMA (total of 12 replies across types I-III) reported that they attend 2–6 appointments per month in connection with their child's SMA, and 6 (50%) estimated they spend over 20 hours per month in connection with these appointments.(11) As the disease progresses, patients require more intensive treatments. The impact on carers' lives was also captured in the survey based on representative comments from family carers regarding the challenges of looking after a child with SMA, as follows (11):

- Parent of young persons aged 16 with SMA type II: The biggest challenge in having a child with SMA is learning to adapt your life to meet the needs of your child. There are not just the physical and emotional demands but the financial demands as well since anything needed for a child with a disability comes with a huge price tag.
- Parent of child age 2 with SMA type II: Turning 4 times a night and monitoring the ventilation up to ten times a night. We always have to take care of the needs of our baby by ourselves and spend countless hours trying to give them the care (physiotherapy) they should be receiving from professionals by ourselves.
- Parent of a young person age 11 with SMA type III: Tiredness, backache, lack of time for myself, lack of time for other child, stress.
- Parent of a child age 19 – 35 months with SMA type I / II (specific age not given): At such a young age the biggest concern for us is our mental preparation for physical deterioration and the problems we will face as a family.
- Parent of a child age 9 with SMA type III: Taking time out of work to attend appointments. Constantly 'pushing' to get what our child needs / not feeling that we are doing enough. Emotional difficulties/distress and extra stress. Extra vigilance, worry and uncertainty about everyday activities and about what the future holds for our child. Challenging to help child be as independent as possible, and to fulfil their potential. Sibling relationship management.

In paediatric conditions, caregivers' HRQoL can be significantly affected in specific ways (e.g. sleep) to which standard HRQoL measures may not be sensitive. No data is available on caregiver utility specific to the health states incorporated in the economic models.

Additionally, more than one caregiver may be affected; in the case of paediatric conditions, this may extend beyond the immediate family. A patient survey conducted in Scotland(11) reported that, out of 19 children and adults with SMA, unpaid care was provided by parents (n=16), grandparents or other relatives (n=11), friends (n=4), a partner (n=1), a son/daughter (n=1) or someone else (relationship not disclosed; n=1). A large proportion of the carers had given up work completely (n=42%) or dropped to part-time (37%) due to their caring responsibilities. Siblings may also be affected in ways which are not usually taken into account in economic evaluation (e.g. impact on school attendance).

Caregiver QALYs are linked to patients' life years, not caregiver life years; analogous to patient QALYs, carer QALYs are calculated as patient life years multiplied by caregiver utilities. This can give rise to potentially counterintuitive results:

- Caregiver utilities can be adversely affected by improved patient survival, resulting in an adverse (and counterintuitive) impact on carer QALYs of improving patient survival.
- Increasing the number of caregivers affected can, paradoxically, result in a deterioration of the ICER.
- An HRQoL adjustment can be made for bereavement but there is little evidence to quantify the magnitude or duration of this effect.
- Caregiver HRQoL impact can be modelled by a positive utility or a utility decrement (a negative amount) but there is no clear guidance on which is more appropriate or how it should be implemented.

There are several options for modelling health benefits of caregivers. carer utilities included in the model submitted to NICE were considered by the ERG to lack face validity. Carer utilities by SMA type from the Bastida et al. (2106) study were used by the ERG but the appraisal committee considered that the ERG's approach lacked face validity whereby the best health state was associated with the worst utility/greatest disutility.

Taking advantage of the caregiver utilities obtained by Bastida et al. (2016), including those from other countries, 'narrow range' and 'wide range' options have been tested. The 'wide range' used in the base case implements the average utility in the Spanish arm of the study (0.484) for the lower bound and the EQ-5D score for the general population of the UK (0.915). The Spanish results are published in a peer-reviewed journal (12) and also had the highest number of respondents out of the 4 countries. The 'narrow range' is used in scenario analyses and implements the upper and lower utilities by SMA type for the UK arm of the study (0.63 and 0.88). Caregiver utilities are shown in Table 15 and are implemented in the economic models as disutilities to the UK general population using the 'wide range' values and 2 caregivers in the base case; the narrow ranges is tested in scenarios.

Identical lower bounds for caregiver utilities in early and later onset have been applied for the 'wide range'. Lower and upper bound utilities in patients and caregivers do not significantly differ in the case vignettes and therefore we have kept the lower and upper bound caregiver utilities equal between early and later onset patients.

Much of the burden to caregivers is emotional and psychological stress which, based on the Scottish SMA survey, seems very burdensome regardless of SMA type. Given the high burden descriptions in the survey, it was not deemed plausible that the worst health state for later onset patients would be equivalent to that of an early onset patient who has significantly improved health as a result of treatment (thus engendering amongst caregivers different expectations as to the disease trajectory). A caregiver of a later onset patient who is in the worst health state is likely to have similar HRQL to that of a caregiver looking after an early onset patient in the worst health state (reflecting the similarity between utility values for early onset and later onset patients in the worst health state).

Between the upper and lower bounds, equal incremental changes in utility are applied as health states progress from worst to best (top to bottom in Table 15). The two best health states in later onset SMA are assigned the same utility, as in the case vignette study.

Table 15. Caregiver utilities for early and later onset SMA

Health state – early onset	Carer utilities: narrow range	Carer utilities: wide range
Early Onset		
No Milestone Achieved	0.630	0.484
Mild Milestones	0.672	0.556
Moderate Milestones	0.713	0.628
Sits Without Support	0.755	0.700
Stands With Assistance	0.797	0.771
Walks With Assistance	0.838	0.843
Stands/Walks Unaided	0.880	0.915
Later Onset		
Sits Without Support But Does Not Roll	0.630	0.484
Sits and Rolls Independently	0.693	0.592
Sits and Crawls With Hands and Knees	0.755	0.700
Stands/Walks With Assistance	0.818	0.807
Stands Unaided	0.880	0.915
Walks Unaided	0.880	0.915

Table 16 and Table 17 show the effect of revised assumptions for caregiver utilities (wide values and a single caregiver). The results presented below were run using the list price of £75,000 per vial and all other assumptions from the original model, in both cases the incremental QALYs are increased and ICERs reduced.

Table 16. Early Onset – Caregiver utilities

Early Onset	Incr. Costs	Incr. QALYs (Patients & caregivers)	ICER (Patients & care-givers)
Original assumption	2,189,113	5.40	404,708
Revised assumption	2,189,113	5.94	368,123

Table 17. Later Onset – Caregiver utilities

Later Onset	Incr. Costs	Incr. QALYs (Patients & caregivers)	ICER (Patients & care-givers)
Original	2,968,464	3.14	945,531
Revised	2,968,464	5.73	518,470

1.5.5 Health state costs

The cost of SMA to the healthcare system is substantial. However, there have been numerous challenges in accurately depicting the true cost of this orphan disease. As is evident from the Scottish SMA survey(11), substantial hidden costs to families and caregivers remain uncaptured. Furthermore, patient experts at the committee meeting in June in addition to clinical advisors to the ERG noted that the health state costs sourced from Bastida et al were significantly underestimated, especially for type I & type II SMA.

In order to more accurately depict the cost of SMA in the UK, Biogen have undertaken the following:

- A RWE survey to substantiate the direct costs of SMA to the UK healthcare system
- An analysis of hospital episode statistic (HES) data in the UK

The existing literature on SMA epidemiology, burden of disease, resource usage and costs is limited from a UK perspective. Available data in these areas are typically either globally focused, overly specific to a niche local setting, or not stratified by SMA subtypes.

1.5.5.1 Health state costs estimated by RWE survey, 2017(13)

A sample of leading paediatric neurological consultants representing nine UK centres completed a survey in 2017 to evaluate best estimates related to these points. The responding centres were treating a total of 272 SMA patients at the time. The survey indicated that:

- The highest overall financial burden was associated with SMA type I, followed by type II and III, each carrying an annual financial burden of £77,968, £55,185 and £20,229, respectively
- The most important contributors to overall disease burden differ by SMA type, with hospital admissions being important in SMA type I, and major clinical interventions (scoliosis surgery) being most important in later onset disease
- As motor function declined, the requirement for ventilation support increased. Furthermore, the requirement for hospital resources (scheduled visits) increased as motor and/or respiratory function worsened
- Treatment practice is variable across centres, with more intensive and more variable treatment typically seen within the large treatment centres.

The survey also confirmed that the patient populations enrolled in the pivotal ENDEAR and CHERISH studies were largely reflective of the UK SMA population; albeit highlighting delays in diagnosis and treatment initiation which occur in the real-world setting. In addition, the relevance of the study outcomes to UK clinical practice was confirmed.

In summary, the survey outcomes support the belief that, while treatment practice refers to international guidelines, the care pathway of any individual patient will be determined according to local practice.

Table 18 below outlines the survey results implemented in the revised model base case, further information on the resource use and unit costs are available in the accompanying report. Original costs from Bastida et al have been assessed in scenario analyses.

Table 18. Health state costs (direct perspective)

SMA type	RWE survey	Bastida et al. (2016)
SMA Type I	£77,968	£18,110
SMA Type II	£55,185	£9,634
SMA Type III	£20,229	£2,806

1.5.5.2 Analysis of Hospital Episode Statistics (HES) data

Hospital Episode Statistics (HES) is a database containing all admissions to NHS hospitals in England, including inpatient, outpatient and accident, and emergency attendances. It collects data for all NHS patients, including private patients treated in NHS hospitals and patients who reside outside of England. With more than 90 million new records each year, HES is a main data source for a wide range of analyses for the NHS, government and many other organizations.

Vantage, database supplied by Health IQ, was used to extract inpatient care costs in NHS hospitals in England using HES at a selected disease area level.

Vantage databases provides access to inpatient attendances from April 2016.

The database was searched to identify relevant patients using ICD-10 codes in two observed periods: April 2016 - March 2017 and April 2017 - March 2018. Patients were selected if the relevant ICD-10 code appeared as their primary or secondary diagnosis, to capture attendances of patients that have the observed disease but were primarily admitted for some other reason. Observed ICD-10 codes are listed below:

- Spinal muscular atrophy, Type I (ICD-10 code: G12.0)
- Spinal muscular atrophy and related syndromes (ICD-10 code: G12)
- Congenital myopathies (ICD-10 code: G71.2).

Only SMA type I has a uniquely defined ICD-10 code, while the coding of other disease types (type II and type III) may vary and be subject to miscoding. Congenital myopathy, a subtype of primary disorders of muscles, was selected as analogue disorder to be indicative of inpatient care costs of patients with later onset SMA.

The database was used to extract the monthly average cost per patient for observed disorders. Tables 14-16 contain data for 1) all admitted patients and 2) patients below 5 years of age. Small number suppression has been applied to all outputs, in accordance with NHS Digital guidelines to protect the privacy and confidentiality of individuals.

Disclaimer: Secondary care data is taken from the English Hospital Episodes Statistics (HES) database produced by the Health and Social Care Information Centre (NHS Digital, http://content.digital.nhs.uk/hes) Copyright; 2017, Re-used with the permission of the Health & Social Care Information Centre. All rights reserved. HES data is released to the general public under the strict guidelines which protect the privacy and confidentiality of patients. All data is small-number suppressed in accordance with NHS Digital guidelines.

Table 19. Spinal muscular atrophy, Type I (ICD-10 code: G12.0) – average monthly cost per patient

HES tariff costs	All age groups	<5 years of age
April 2016-March 2017	£3,280	£3,012
April 2017-March 2018	£4,095	£4,237

Table 20.Spinal muscular atrophy and related syndromes (ICD-10 code: G12) - average monthly cost per patient

HES tariff costs	All age groups	<5 years of age
April 2016-March 2017	£3,132	£4,362
April 2017-March 2018	£3,440	£5,490

Table 21.Congenital myopathies (ICD-10 code: G71.2) - average monthly cost per patient

HES tariff costs	All age groups	<5 years of age
April 2016-March 2017	£3,204	£5,563
April 2017-March 2018	£3,991	£5,563

Costs reported above whilst only encompassing inpatient care (i.e. GP & outpatient attendances are omitted) support the statements from the Scottish SMA survey(11) and those from patient experts at the appraisal committee meeting in June regarding the significantly underestimated health state costs reported in Bastida et al. (2016). Costs reported in Bastida et al. (2016) are based on self-response of 34 caregivers in the UK, thus represent only a subset of total patient population. Caregivers provided data regarding the volume of care. Total costs were obtained by multiplying resource use with the average unit costs. Inpatient attendances, one of the major drivers of health care costs, are usually very complex and therefore very costly for SMA patients. Without knowing the exact procedure provided, the average cost of hospital attendance will be a poor representation of the true cost of the treatment and highly downward biased. Therefore, taking into account above presented arguments, we believe that RWE survey provides better estimates of health state costs across all SMA types.

Table 16 and Table 23 show the effect of revised assumptions for health state costs. The results presented below were run using the list price of £75,000 per vial and all other assumptions from the original model. In the early onset model, incremental costs are increased reflecting higher cost of managing type I SMA coupled with the critiqued highly optimistic survival and trajectory assumptions in the original model, accruing additional management costs. In the later onset model, costs are reduced as more patients achieve higher milestones which are associated with lower annual management costs.

Table 22. Early Onset – Health state costs

Early Onset	Incr. Costs	Incr. QALYs (Patients)	ICER (Patients)
Original assumption (Bastida)	2,189,113	5.34	409,981
Revised assumption (RWE)	2,256,810	5.34	417,224

Table 23. Later Onset – Health state costs

Later Onset	Incr. Costs	Incr. QALYs (Patients)	ICER (Patients)
Original assumption (Bastida)	2,968,464	2.24	1,325,526
Revised assumption (RWE)	2,759,598	2.24	1,232,260

1.5.6 Additional modifications

In addition to the major revisions above, other minor adaptations have been implemented in the model addressing ERG critique, including:

- Initial distribution across health states were set equal to the weighted average probability (aligned with ERG analyses) of being in each state in both groups at baseline in ENDEAR and CHERISH for the early and later onset models, respectively.
- End of life costs have been applied in the later onset model, consistent with the early onset model
- Due to lack of evidence and high mortality rates with usual care, assumptions regarding the proportion of early onset patients expected to have scoliosis surgery and the proportion of patients expected to discontinue treatment following scoliosis surgery has been aligned with the later onset model.

1.6 Proposed commercial offer

Following the appraisal consultation, Biogen has revised the commercial offer for nusinersen dependent on commissioning being agreed across both early and later onset SMA to reduce the ICERs and also mitigate risk to the NHS to ensure access is both managed and sustainable. The offer includes the following:

[redacted]

1.7 Updated Results

1.7.1 Methods in early onset model

Biogen undertook a set of exploratory analyses applied to early onset model. The preferred analysis includes: (i) the use of a common initial distribution across health states for both treatment groups; (ii) 1% nusinersen patients worsen each cycle and follow the usual care transition matrix; (iii) the inclusion of health state costs estimated by RWE survey, 2017; (iv) the inclusion of scoliosis assumptions aligned with later onset; (v) the use of patient utilities from Lloyd et al. (vignette study); (vi) the use of "wide range" caregiver utilities and (vii) the inclusion of 2 caregivers. Additionally, the early onset model also included: (i) no mortality adjustment factor and (ii) HR tapered over 60 months period. All analyses were undertaken by assuming (i) £75,000 nusinersen vial price and the commercial offer using the deterministic version of the revised cost-effectiveness model.

Additional sensitivity analyses were performed to explore: (i) longer tapering period of the treatment effect in the early onset model; (ii) alternative assumptions regarding mortality adjustment; (iii) alternative assumptions regarding long-term transition probabilities; (iv) patient subgroups based on disease duration; (v) alternative assumptions regarding health state costs; (vi) patient utilities and (vii) caregiver utilities.

The methods used to implement these analyses in the early onset model are described below.

Exploratory analysis 1: slower rate of decline in CHOP-INTEND for the usual care arm

In this scenario, a mean monthly rate of CHOP-INTEND decline of 0.11 was used instead of [redacted] in the base case.

Exploratory analysis 2: Longer tapering period of the treatment effect in the early onset model

In this scenario, HR was tapered over a period of 120 month instead of 60, as in the base case.

Exploratory analysis 3: Use of alternative mortality adjustment factors

No mortality adjustment was assumed in the base case, in scenarios this was applied and set to 0.5 when modelling nusinersen-treated patients in the better health states.

Exploratory analysis 4-6: Alternative assumptions regarding long-term transition probabilities

Three additional scenarios were undertaken using the company's base case to explore the impact of long-term probabilities (post-trial follow-up) on the on the cost-effectiveness of nusinersen versus usual care: (i) 2% of patients stop improving and follow RWC transition matrix, (ii) 1% of patients stop improving and lose 1 milestone per cycle and (iii) no patients worsen (except for discontinuation due to scoliosis surgery)

Exploratory analysis 7-8: Patient subgroups based on disease duration

Cost-effectiveness of nusinersen vs. standard care was examined for 2 patient subgroups based on the disease duration. Patient groups included those that had symptom onset before 12 weeks of age and after 12 weeks of age.

Exploratory analysis 9: Use of health state costs from Bastida et al. (2016)

Analyses using Bastida et al (2016) health state costs were applied as shown in Table 18.

Exploratory analysis 10-11: Alternative assumptions regarding patient utilities

Two alternative analyses were undertaken to explore the impact of using different HRQoL estimates for patients with SMA: (i) analysis using utilities reported by the ERG clinical advisors and (ii) analysis using the PedsQL data collected as part of the CHERISH study. Table 12 presents the values for both scenarios.

Exploratory analysis 12: Alternative assumptions regarding caregiver utilities

In order to address uncertainty in caregiver utilities, additional scenario was explored for both cost-effectiveness models. This “narrow range” uses the upper and lower utilities by SMA type as reported in Bastida et al. (2016). Between the upper and lower bounds, equal incremental changes in utility are applied as health states progress from worst to best as presented in Table 15.

[redacted]

[redacted]

1.7.2 Results of the exploratory analyses – early onset SMA

The results of the company’s base case and exploratory analyses are shown in Table 24 for £75,000 vial price and Table 25 for the commercial offer.

The base case scenario at £75,000 vial price has an ICER of £895,865 per QALY gained for patients and £684,389 per QALY gained including patient health gains and caregiver QALY losses. Respective numbers implementing the commercial offer are[redacted] per QALY gained for patients and[redacted] per QALY including caregiver perspective. Extending the tapering period of the treatment effect has a moderate effect on the ICER, driven by higher QALY gain in nusinersen arm. Use of the more optimistic assumption regarding later onset mortality, yields an additional 0.72 QALYs for nusinersen-treated patients and decreases the ICER markedly (£693,615 per QALY – patient perspective, £626,825 per QALY - patient and caregiver perspective at £75,000 vial price and [redacted] per QALY – patient perspective, [redacted] per QALY - patient and caregiver perspective at the commercial offer). If an additional 1% of patients worsen each cycle or follow a pessimistic scenario where they lose 1 milestone a cycle (or 3 per year) the ICERs markedly increase, driven by the lower QALY gain in the treatment arm.

Patients with shorter disease duration (<=12 weeks) accrue markedly more QALYs compared to the other subgroup (1.19 vs. 0.12 QALYs) which had a significant impact on the cost-effectiveness of nusinersen. The use of health state costs from Bastida et al. (2016) moderately lowers the ICER in all cases. Similarly, use of alternative scenarios for patient utilities lowers the ICERs, especially in the case of utilities reported by the ERG clinical advisors where QALY gains increase by 0.41 with nusinersen. Finally, the use of “narrow range” caregiver utilities increases the ICER (£638,574 per QALY - patient and caregiver perspective at £75,000 vial price and[redacted] - patient and caregiver perspective at the commercial offer[redacted]

Table 24. Early onset model exploratory analyses, list price

Option	QALYs (patient)	QALYs (patient+ caregiver)	Cost	Inc. QALYs (patient)	Inc. QALYs (patient+ caregiver)	Inc. cost	ICER (patient)	ICER (patient+ caregiver)
Revised model base case								
Nusinersen	0.57	-0.96	£1,116,254	1.05	1.37	£940,146	£895,865	£684,389
Usual care	-0.48	-2.34	£176,108	-	-	-	-	-
S1 – Slower usual care arm decline in CHOP-INTEND								
Nusinersen	0.65	-0.80	£1,111,677	1.12	1.50	£935,569	£835,214	£621,804
Usual care	-0.47	-2.31	£176,108	-	-	-	-	-
S2 – 120 months tapering period of the treatment effect								
Nusinersen	0.79	-0.77	£1,204,057	1.27	1.57	£1,027,949	£808,890	£656,434
Usual care	-0.48	-2.34	£176,108	-	-	-	-	-
S3 – Later onset mortality adjustment applied (0.5)								
Nusinersen	1.29	-0.38	£1,401,513	1.77	1.95	£1,225,405	£693,615	£626,825
Usual care	-0.48	-2.34	£176,108	-	-	-	-	-
S4 – 2% of patients worsen and follow RWC transition matrix								
Nusinersen	0.44	-1.19	£1,079,622	0.92	1.14	£903,514	£983,245	£789,476
Usual care	-0.48	-2.34	£176,108	-	-	-	-	-
S5 – 1% of patients worsen and lose 1 milestone per cycle								
Nusinersen	0.56	-0.98	£1,116,657	1.04	1.35	£940,549	£904,746	£694,673
Usual care	-0.48	-2.34	£176,108	-	-	-	-	-
S6 – no patients worsen (except discontinuation due to scoliosis surgery)								
Nusinersen	0.73	-0.69	£1,159,351	1.21	1.65	£983,243	£815,847	£596,567
Usual care	-0.48	-2.34	£176,108	-	-	-	-	-
S7 – <= 12 weeks disease duration								
Nusinersen	1.19	-0.01	£1,263,781	1.67	2.36	£1,087,361	£649,579	£459,996
Usual care	-0.49	-2.37	£176,420	-	-	-	-	-
S8 – > 12 weeks disease duration								
Nusinersen	0.12	-1.72	£1,004,210	0.59	0.58	£828,381	£1,397,060	£1,419,462
Usual care	-0.47	-2.31	£175,829	-	-	-	-	-
S9 – Health state costs form Bastida et al. (2016)								
Nusinersen	0.57	-0.96	£959,927	1.05	1.37	£910,790	£867,891	£663,018
Usual care	-0.48	-2.34	£49,138	-	-	-	-	-
S10 – ERG clinical advisors' patient utilities								
Nusinersen	1.91	0.38	£1,116,254	1.46	1.79	£940,146	£642,965	£526,256

Option	QALYs (patient)	QALYs (patient+ caregiver)	Cost	Inc. QALYs (patient)	Inc. QALYs (patient+ caregiver)	Inc. cost	ICER (patient)	ICER (patient+ caregiver)
Usual care	0.45	-1.41	£176,108	-	-	-	-	-
S11 – PedsQL patient utilities								
Nusinersen	2.84	1.30	£1,116,254	1.27	1.60	£940,146	£738,433	£588,534
Usual care	1.56	-0.30	£176,108	-	-	-	-	-
S12 – "Narrow range" caregiver utilities								
Nusinersen	0.57	-0.60	£1,116,254	1.05	1.14	£940,146	£895,865	£826,349
Usual care	-0.48	-1.74	£176,108	-	-	-	-	-
[redacted]								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 25. Early onset model exploratory analyses with commercial offer

Option	QALYs (patient)	QALYs (patient+ caregiver)	Cost	Inc. QALYs (patient)	Inc. QALYs (patient+ caregiver)	Inc. cost	ICER (patient)	ICER (patient+ caregiver)
Revised model base case								
Nusinersen	0.57	-0.96	[redacted]	1.05	1.37	[redacted]	[redacted]	[redacted]
Usual care	-0.48	-2.34	[redacted]	-	-	-	-	-
S1 – Slower usual care arm decline in CHOP-INTEND								
Nusinersen	0.65	-0.80	[redacted]	1.12	1.50	[redacted]	[redacted]	[redacted]
Usual care	-0.47	-2.31	[redacted]	-	-	-	-	-
S2 – 120 months tapering period of the treatment effect								
Nusinersen	0.79	-0.77	[redacted]	1.27	1.57	[redacted]	[redacted]	[redacted]
Usual care	-0.48	-2.34	[redacted]	-	-	-	-	-
S3 – Later onset mortality adjustment applied (0.5)								
Nusinersen	1.29	-0.38	[redacted]	1.77	1.95	[redacted]	[redacted]	[redacted]
Usual care	-0.48	-2.34	[redacted]	-	-	-	-	-
S4 – 2% of patients worsen per cycle and follow RWC transition matrix								
Nusinersen	0.44	-1.19	[redacted]	0.92	1.14	[redacted]	[redacted]	[redacted]
Usual care	-0.48	-2.34	[redacted]	-	-	-	-	-
S5 – 1% of patients worsen per cycle and lose 1 milestone per cycle								
Nusinersen	0.56	-0.98	[redacted]	1.04	1.35	[redacted]	[redacted]	[redacted]
Usual care	-0.48	-2.34	[redacted]	-	-	-	-	-
S6 – no patients worsen (except discontinuation due to scoliosis surgery)								
Nusinersen	0.73	-0.69	[redacted]	1.21	1.65	[redacted]	[redacted]	[redacted]
Usual care	-0.48	-2.34	[redacted]	-	-	-	-	-
S7 – <= 12 weeks disease duration								
Nusinersen	1.19	-0.01	[redacted]	1.67	2.36	[redacted]	[redacted]	[redacted]
Usual care	-0.49	-2.37	[redacted]	-	-	-	-	-
S8 – > 12 weeks disease duration								
Nusinersen	0.12	-1.72	[redacted]	0.59	0.58	[redacted]	[redacted]	[redacted]
Usual care	-0.47	-2.31	[redacted]	-	-	-	-	-
S9 – Health state costs form Bastida et al. (2016)								
Nusinersen	0.57	-0.96	[redacted]	1.05	1.37	[redacted]	[redacted]	[redacted]
Usual care	-0.48	-2.34	[redacted]	-	-	-	-	-
S10 – ERG clinical advisors' patient utilities								
Nusinersen	1.91	0.38	[redacted]	1.46	1.79	[redacted]	[redacted]	[redacted]

Option	QALYs (patient)	QALYs (patient+ caregiver)	Cost	Inc. QALYs (patient)	Inc. QALYs (patient+ caregiver)	Inc. cost	ICER (patient)	ICER (patient+ caregiver)
Usual care	0.45	-1.41	[redacted]	-	-	-	-	-
S11 – PedsQL patient utilities								
Nusinersen	2.84	1.30	[redacted]	1.27	1.60	[redacted]	[redacted]	[redacted]
Usual care	1.56	-0.30	[redacted]	-	-	-	-	-
S12 – "Narrow range" caregiver utilities								
Nusinersen	0.57	-0.60	[redacted]	1.05	1.14	[redacted]	[redacted]	[redacted]
Usual care	-0.48	-1.74	[redacted]	-	-	-	-	-
[redacted]								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

1.7.3 Methods in later onset model

Biogen undertook a set of exploratory analyses applied to later onset model. The preferred analysis includes: (i) the use of a common initial distribution across health states for both treatment groups; (ii) 1% nusinersen patients worsen each cycle and follow the usual care transition matrix; (iii) the inclusion of health state costs estimated by RWE survey, 2017; (iv) the inclusion of end-of-life costs; (v) the use of patient utilities from Lloyd et al. (vignette study); (vi) the use of "wide range" caregiver utilities and (vii) the inclusion of 2 caregivers. All analyses were undertaken by assuming (i) £75,000 nusinersen vial price and the commercial offer using the deterministic version of the revised cost-effectiveness model.

Additional sensitivity analyses were performed to explore: (i) a slower rate of HFMSE decline in the usual care arm; (ii) alternative assumptions regarding application of the mortality adjustment; (iii) alternative assumptions regarding long-term transition probabilities; (iv) patient subgroups based on disease duration; (v) alternative assumptions regarding health state costs; (vi) patient utilities and (vii) caregiver utilities.

The methods used to implement these analyses in the early onset model are described below.

Exploratory analysis 1: slower rate of decline in HFMSE for the usual care arm

In this scenario, a slow rate of HFMSE decline 0.05 was assessed compared to [redacted] in the base case.

Exploratory analysis 2: Use of alternative mortality adjustment factors

In the later onset, the model adjustment factor was set to 0.5 instead of 0 (base case i.e. not applied) for nusinersen-treated patients who achieve better motor milestones.

Exploratory analysis 3-5: Alternative assumptions regarding long-term transition probabilities

Three additional scenarios were undertaken using the company's base case to explore the impact of long-term probabilities (post trail follow-up) on the on the cost-effectiveness of nusinersen versus usual care: (i) 2% of patients stop improving and follow RWC transition matrix, (ii) 1% of patients stop improving and lose 1 milestone per cycle and (iii) no patients worsen (except for discontinuation due to scoliosis surgery)

Exploratory analysis 6-7: Patient subgroups based on disease duration

Cost-effectiveness of nusinersen vs. standard care was examined for 2 patient subgroups based on the disease duration for both models. In the later onset model, patient groups were defined based on a 25-month threshold.

Exploratory analysis 8: Use of health state costs from Bastida et al. (2016)

Analyses using Bastida et al (2016) health state costs were applied as shown in Table 18.

Exploratory analysis 9-10: Alternative assumptions regarding patient utilities

Two alternative analyses were undertaken to explore the impact of using different HRQoL estimates for patients with SMA: (i) analysis using utilities reported by the ERG clinical advisors and (ii) analysis using the PedsQL data collected as part of the CHERISH study (Table 12).

Exploratory analysis 11: Alternative assumptions regarding caregiver utilities

In order to address uncertainty in caregiver utilities, additional scenario was explored for both cost-effectiveness models. This "narrow range" uses the upper and lower utilities by SMA type as reported in Bastida et al. (2016). Between the upper and lower bounds, equal incremental changes in utility are applied as health states progress from worst to best. The two best health states in later onset SMA are assigned the same utility, as in the case vignette study. Table 15 presents caregiver utilities for later onset models.

1.7.4 Results of the exploratory analyses – later onset SMA

The results of the company's base case and exploratory analyses are shown in Table 26 for £75,000 vial price and Table 27 for the commercial offer.

Base case scenario at £75,000 vial price has an ICER of £394,343 per QALY gained for patients and £174,106 per QALY gained including patient health gains and caregiver QALY losses. Respective numbers at the commercial offer are [redacted] per QALY gained for patients and [redacted] per QALY gained including the caregiver perspective. Application of the more optimistic assumption regarding later onset mortality, slightly reduces the ICER. Similarly, if the RWC decline is slower, the ICER is marginally reduced. In contrast if more patients deteriorate per cycle or follow a faster trajectory of losing 1 milestone a cycle (or 3 a year), the ICERs markedly increase.

Nusinersen is more cost-effective in a patient subgroup with shorter disease duration (< 25 months, [redacted] at £75,000 and[redacted] at the commercial offer), while the opposite stands for the group with longer disease duration (>=25 months). The use of health state costs from Bastida et al. (2016) moderately increases the ICER in all cases. Further, alternative assumptions for patient utilities significantly increase the ICER. That is particularly evident when PedsQL patient utilities are used in the model. Lastly, the use of "narrow range" caregiver utilities has a moderate positive effect on the ICER (£228,742 per QALY - patient and caregiver perspective at £75,000 vial price and[redacted] - patient and caregiver perspective at the commercial offer)

Table 26 - Later onset model exploratory analyses, list price

Option	QALYs (patient)	QALYs (patient+ caregiver)	Cost	Inc. QALYs (patient)	Inc. QALYs (patient+ caregiver)	Inc. cost	ICER (patient)	ICER (patient+ caregiver)
Revised model base case								
Nusinersen	5.83	-3.56	£2,943,909	4.74	10.74	£1,869,905	£394,343	£174,106
Usual care	1.09	-14.30	£1,074,004	-	-	-	-	-
S1 – slower usual care arm decline in HFMSE								
Nusinersen	6.05	-3.05	£2,933,540	4.89	10.97	£1,862,122	£380,476	£169,709
Usual care	1.15	-14.02	£1,071,419	-	-	-	-	-
S2 – Type III mortality adjustment applied (0.5)								
Nusinersen	6.29	-3.22	£3,079,924	5.21	11.08	£2,005,549	£385,233	£181,009
Usual care	1.09	-14.30	£1,074,375	-	-	-	-	-
S3 – 2% of patients worsen per cycle and follow RWC transition matrix								
Nusinersen	4.93	-5.34	£2,601,589	3.84	8.96	£1,527,586	£397,590	£170,577
Usual care	1.09	-14.30	£1,074,004	-	-	-	-	-
S4 – 1% of patients worsen per cycle and lose 1 milestone per cycle								
Nusinersen	5.10	-5.74	£2,976,199	4.01	8.56	£1,902,195	£474,009	£222,214
Usual care	1.09	-14.30	£1,074,004	-	-	-	-	-
S5 – no patients worsen (except for discontinuation due to scoliosis surgery)								
Nusinersen	7.31	-0.70	£3,563,559	6.22	13.60	£2,489,556	£400,359	£183,114
Usual care	1.09	-14.30	£1,074,004	-	-	-	-	-
S6 – < 25 months disease duration								
Nusinersen	8.33	2.25	£3,541,105	7.32	16.98	£2,464,096	£336,836	£145,083
Usual care	1.02	-14.74	£1,077,009	-	-	-	-	-
S7 – >= 25 months disease duration								
Nusinersen	5.63	-4.36	£2,671,536	3.47	7.26	£1,645,956	£474,964	£226,870
Usual care	2.17	-11.62	£1,025,580	-	-	-	-	-
S8 – Health state costs form Bastida et al. (2016)								
Nusinersen	5.83	-3.56	£2,248,397	4.74	10.74	£2,057,797	£433,968	£191,601
Usual care	1.09	-14.30	£190,600	-	-	-	-	-
S9– ERG clinical advisors' patient utilities								
Nusinersen	13.58	4.20	£2,943,909	1.74	7.74	£1,869,905	£1,076,164	£241,722
Usual care	11.85	-3.54	£1,074,004	-	-	-	-	-
S10 – PedsQL patient utilities								

Nusinersen	15.35	5.96	£2,943,909	0.89	6.88	£1,869,905	£2,112,435	£271,655
Usual care	14.46	-0.92	£1,074,004	-	-	-	-	-
S11 – "Narrow range" caregiver utilities								
Nusinersen	5.83	-0.98	£2,943,909	4.74	8.17	£1,869,905	£394,343	£228,742
Usual care	1.09	-9.15	£1,074,004	-	-	-	-	-

Table 27. Later onset model exploratory analyses, commercial offer

Option	QALYs (patient)	QALYs (patient+ caregiver)	Cost	Inc. QALYs (patient)	Inc. QALYs (patient+ caregiver)	Inc. cost	ICER (patient)	ICER (patient+ caregiver)
Revised model base case								
Nusinersen	5.83	-3.56	[redacted]	4.74	10.74	[redacted]	[redacted]	[redacted]
Usual care	1.09	-14.30	[redacted]	-	-	-	-	-
S1 – slower usual care arm decline in HFMSE								
Nusinersen	6.05	-3.05	[redacted]	4.89	10.97	[redacted]	[redacted]	[redacted]
Usual care	1.15	-14.02	[redacted]	-	-	-	-	-
S2 – Type III mortality adjustment applied (0.5)								
Nusinersen	6.29	-3.22	[redacted]	5.21	11.08	[redacted]	[redacted]	[redacted]
Usual care	1.09	-14.30	[redacted]	-	-	-	-	-
S3 – 2% of patients worsen per cycle and follow RWC transition matrix								
Nusinersen	4.93	-5.34	[redacted]	3.84	8.96	[redacted]	[redacted]	[redacted]
Usual care	1.09	-14.30	[redacted]	-	-	-	-	-
S4 – 1% of patients worsen per cycle and lose 1 milestone per cycle								
Nusinersen	5.10	-5.74	[redacted]	4.01	8.56	[redacted]	[redacted]	[redacted]
Usual care	1.09	-14.30	[redacted]	-	-	-	-	-
S5 – no patients worsen (except for discontinuation due to scoliosis surgery)								
Nusinersen	7.31	-0.70	[redacted]	6.22	13.60	[redacted]	[redacted]	[redacted]
Usual care	1.09	-14.30	[redacted]	-	-	-	-	-
S6 – < 25 months disease duration								
Nusinersen	8.33	2.25	[redacted]	7.32	16.98	[redacted]	[redacted]	[redacted]
Usual care	1.02	-14.74	[redacted]	-	-	-	-	-
S7 – >= 25 months disease duration								
Nusinersen	5.63	-4.36	[redacted]	3.47	7.26	[redacted]	[redacted]	[redacted]
Usual care	2.17	-11.62	[redacted]	-	-	-	-	-
S8 – Health state costs form Bastida et al. (2016)								
Nusinersen	5.83	-3.56	[redacted]	4.74	10.74	[redacted]	[redacted]	[redacted]
Usual care	1.09	-14.30	[redacted]	-	-	-	-	-
S9– ERG clinical advisors' patient utilities								
Nusinersen	13.58	4.20	[redacted]	1.74	7.74	[redacted]	[redacted]	[redacted]
Usual care	11.85	-3.54	[redacted]	-	-	-	-	-
S10 – PedsQL patient utilities								
Nusinersen	15.35	5.96	[redacted]	0.89	6.88	[redacted]	[redacted]	[redacted]

Usual care	14.46	-0.92	[redacted]	-	-	-	-	-
S11 – "Narrow range" caregiver utilities								
Nusinersen	5.83	-0.98	[redacted]	4.74	8.17	[redacted]	[redacted]	[redacted]
Usual care	1.09	-9.15	[redacted]	-	-	-	-	-

1.8 Conclusions & closing remarks

Biogen appreciates the continued engagement by NICE and NHSE in this STA process. During the January meeting between Biogen, NICE & NHS England it was widely acknowledged that when assessing the first DMT in a rare disease, affecting primarily paediatric patients, flexibility would be required in the STA process to truly evaluate the benefit to patients and whether these benefits translate into a good use of NHS resource. The assessment is further complicated by the fact that nusinersen was accelerated through the European regulatory process where the clinical trials were closed earlier than planned on ethical grounds, given the proven positive benefit during the interim analysis of nusinersen in patients with a significant unmet need. Recognising the challenge of assessing an orphan medicine such as nusinersen through the NICE STA appraisal process, Biogen asks that the following factors be considered within a [redacted] managed access agreement (MAA) in reaching a decision:

- Nusinersen is unusual for an orphan medicine in that its efficacy & safety is supported by two large randomised, phase III clinical trials. These trials were stopped early on ethical grounds given the proven positive benefit during the interim analysis of nusinersen in patients with a significant unmet need.
    - **Biogen continue to measure the long-term outcomes of patients on nusinersen in our ongoing clinical trial programme e.g. SHINE, which will supplement long-term clinical data collected under an MAA.**
- Quality of Life of Patients: Published literature and the NICE appraisal committee have acknowledged the difficulties in measuring quality of life in a paediatric patient population. There are also specific challenges related to assessing quality of life in this patient population (particularly with type I patients) with nusinersen:
    - Partly because of the difficulties of measuring HRQoL in children, no measures were included in the ENDEAR trial
    - The health states defined in the model are based on gross motor functions and may therefore neglect changes in fine motor functions which can be important to patients with SMA
    - Where treatment is expected to improve survival (particularly in type I patients) beyond the normal life expectancy of patients with SMA, there is no experience on which to base HRQoL assessments
    - **Nevertheless, quality of life will be collected using during the period of the MAA**
- Quality of Life of Caregivers: No data is available on caregiver utility specific to the health states incorporated in the economic models. More than one caregiver may be affected; in the case of paediatric conditions, this may extend beyond the immediate family. Caregiver QALYs are linked to patients' life years, not caregiver life years, potentially yielding counterintuitive results
    - **Biogen therefore believe that the impact on quality of life of at least two carers should be considered when considering the impact of nusinersen. Quality of Life for carers are proposed for collection during the period of the MAA**

Value for Money

- **As well as factors that should be included in the NICE assessment, Biogen ask NHS England to consider the impact of nusinersen on other factors not included in the NICE assessment. These factors include the potential impact on loss of employment & productivity for both the patient, families and carers impacted**

[redacted]

[redacted]

[redacted]

1.9 References

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1.10 Annex: Transition matrices nusinersen arm after trial follow-up

Table 28. Nusinersen transition matrix after trial follow up (patients keep improving) – Early onset

		Next period's health state						
		No Milestones	Mild Milestones	Moderate Milestones	Sits without support	Stands with assistance	Walks with assistance	Stands/ walks unaided
Current health states	No Milestones	[redacted]						
	Mild Milestones		[redacted]	[redacted]				
	Moderate Milestones			[redacted]	[redacted]			
	Sits without support				[redacted]	[redacted]		
	Stands with assistance					[redacted]	[redacted]	
	Walks with assistance						[redacted]	[redacted]
	Stands/ walks unaided							[redacted]

Table 29. Nusinersen transition matrix after trial follow up (patients keep improving) – Later onset

		Next period's health state					
		Sits without support but does not rolls	Sits and rolls independently	Sits and crawls with hands and knees	Stands/walks with assistance	Stands Unaided	Walks unaided
Current health states	Sits without support but does not rolls	[redacted]					
	Sits and rolls independently		[redacted]	[redacted]			
	Sits and crawls with hands and knees				[redacted]		
	Stands/walks with assistance				[redacted]	[redacted]	
	Stands Unaided					[redacted]	[redacted]
	Walks unaided						[redacted]

Table 30. Patients remaining in the same health state – Early onset

		Next period's health state						
		No Milestones	Mild Milestones	Moderate Milestones	Sits without support	Stands with assistance	Walks with assistance	Stands/ walks unaided
Current health states	No Milestones	100%						
	Mild Milestones		100%					
	Moderate Milestones			100%				
	Sits without support				100%			
	Stands with assistance					100%		
	Walks with assistance						100%	
	Stands/ walks unaided							100%

*Same approach used for later onset

Table 31. RWC transition matrix after trial follow up (patients worsening) –Early onset

		Next period's health state						
		No Milestones	Mild Milestones	Moderate Milestones	Sits without support	Stands with assistance	Walks with assistance	Stands/ walks unaided
Current health states	No Milestones	[redacted]						
	Mild Milestones	[redacted]	[redacted]					
	Moderate Milestones		[redacted]	[redacted]				
	Sits without support			[redacted]				
	Stands with assistance				[redacted]			
	Walks with assistance					[redacted]	[redacted]	
	Stands/ walks unaided						[redacted]	[redacted]

Table 32. RWC transition matrix after trial follow up (patients worsening) – Later onset

		Next period's health state					
		Sits without support but does not rolls	Sits and rolls independently	Sits and crawls with hands and knees	Stands/walks with assistance	Stands Unaided	Walks unaided
Current health states	Sits without support but does not rolls	[redacted]					
	Sits and rolls independently	[redacted]	[redacted]				
	Sits and crawls with hands and knees		[redacted]	[redacted]			
	Stands/walks with assistance			[redacted]	[redacted]		
	Stands Unaided				[redacted]	[redacted]	
	Walks unaided					[redacted]	[redacted]

Table 33. All patients worsening lose one milestone at each cycle (alternative scenario) – Early onset

		Next period's health state						
		No Milestones	Mild Milestones	Moderate Milestones	Sits without support	Stands with assistance	Walks with assistance	Stands/ walks unaided
Current health states	No Milestones	100%						
	Mild Milestones	100%						
	Moderate Milestones		100%					
	Sits without support			100%				
	Stands with assistance				100%			
	Walks with assistance					100%		
	Stands/ walks unaided						100%	

*Same approach used for later onset

Nusinersen for treating spinal muscular atrophy: A Single Technology Appraisal

Addendum - ERG commentary on company's ACD response

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1. Background

In August 2018, the National Institute for Health and Care Excellence (NICE) issued its Appraisal Consultation Document (ACD)[1] which made the following recommendation: *"Nusinersen is not recommended, within its marketing authorisation, for treating 5q spinal muscular atrophy."*

In response to the ACD, the company submitted the following to NICE: (i) an overall ACD response document;[2] (ii) a supplementary appendix reporting data from the ENDEAR and SHINE studies;[3] (iii) a supplementary appendix detailing modifications to the company's original early and later onset SMA models, including a new commercial access agreement,[4] and (iv) the revised executable models. The company's proposed commercial access agreement is summarised in Box 1. [redacted]

Box 1: Details of the company's proposed commercial access agreement (reproduced from company's ACD response, Supplementary Appendix 2)

[redacted]

This ERG addendum provides the following:

(i) A brief summary and critique of the additional evidence from the ENDEAR and SHINE studies (Section 2)

(ii) A summary of the company's model amendments and new base case incremental cost-effectiveness ratios (ICERs) (Section 3.1)

(iii) Verification work undertaken by the ERG to check the integrity of the new model structures and to assess whether the commercial offer has been applied correctly (Section 3.2)

(iv) A summary and critique of the modified assumptions and input data applied within the company's new base case models (Section 3.3)

(v) Additional exploratory analyses surrounding key uncertainties using the company's new models (Section 4).

2. Summary and critique of additional evidence from the ENDEAR and SHINE studies

2.1 Summary of additional evidence from ENDEAR

Supplementary Appendix 1 of the company's ACD response[3] contains new data on hospitalisations and ventilation support from a more recent analysis of the ENDEAR trial.

At 6 months, the adjusted annualised hospitalisation rate (AAHR) was marginally lower in the nusinersen group compared with the sham control group, although the difference did not reach statistical significance (rate ratio 0.759, 95% confidence interval [CI] 0.548 to 1.051, p=0.965; Supplementary Appendix 1,[3] Figure 5A). The main reason for hospitalisation in both groups was respiratory events (59% and 64% in the nusinersen and sham control groups, respectively). The AAHR for respiratory events was slightly lower in the nusinersen group than the sham control group, although this difference was not statistically significant (rate ratio 0.713, 95% CI 0.480 to 1.057, p=0.0919; Supplementary Appendix 1,[3] Figure 5B). The overall time spent hospitalised was significantly lower in the nusinersen group (least squares mean [LSM] 0.114) than the sham group (LSM 0.207; LSM treatment difference -0.093, 95% CI -0.151 to -0.034, p=0.0022), as was the proportion of time spent hospitalised for respiratory reasons (8.71% and 17.35%, respectively; LSM treatment difference -8.638%, 95% CI -14.190 to -3.086, p=0.0026).

No patients in either group required permanent ventilation at baseline. A significantly greater proportion of patients in the nusinersen group survived without permanent ventilation at the end of the study (odds ratio [OR] 3.40, 95% CI 1.535 to 7.553, p=0.0026), and had a significantly reduced risk of requiring permanent ventilation (30%, p=0.0011) than patients in the sham control group.

At baseline, 26% of patients in the nusinersen group and 15% of patients in the sham control group required ventilation support (≥1 hour per day). Among the 74% and 85% of patients, respectively, not

receiving ventilation support at baseline, 25% of patients in the nusinersen group and 3% of patients in the sham control group did not require the initiation of ventilation support while on study (OR 11.6, 95% CI 1.5 to 92.1, *p*=0.021).

There were no statistically significant differences in the adjusted annualised rate of serious respiratory adverse events during the study (rate ratio 0.620, 95% CI 0.374 to 1.029, *p*=0.0643), the LSM percentage of time on respiratory support at the end of the study (LSM treatment difference -6.8, 95% CI -17.8 to 4.2, *p*=0.2233), or the number of days requiring ventilation support ≥16 hours/day at the end of the study (LSM treatment difference -10.402, 95% CI -50.5811 to 29.7763, *p*=0.6091).

2.2 Summary of new evidence from SHINE

Supplementary Appendix 1 of the company's ACD response[3] also contains data on motor function and ventilation-free survival from a more recent interim analysis of SHINE (data cut-off 30 June 2017).

Mean HINE-2 motor milestone total score increased to the last observed visit (day 698) in patients who received nusinersen in ENDEAR and SHINE (mean change 7.4, 95% CI 4.12 to 10.70), and also in patients who received nusinersen in SHINE and sham treatment in ENDEAR (day 302 of nusinersen; mean change 1.2, 95% CI 0.02 to 2.31), and decreased to the last observed visit (day 394) in patients who received sham control treatment in ENDEAR (mean change -0.4, 95% CI -1.52 to 0.68; Supplementary Appendix 1,[3] Figure 1A). Similarly, mean CHOP INTEND score increased to the last observed visit (day 698) in patients who received nusinersen in ENDEAR and SHINE (mean change 16.9, 95% CI 11.9 to 21.9), and also in patients who received nusinersen in SHINE and sham treatment in ENDEAR (day 302 of nusinersen; mean change 3.6, 95% CI -0.9 to 8.1), and decreased to the last observed visit (day 394) in patients who received sham control treatment in ENDEAR (mean change -12.0, 95% CI -17.7 to -6.3; Supplementary Appendix 1,[3] Figure 1B).

A decreasing proportion of patients who received nusinersen in ENDEAR and SHINE met the HINE-2 response criteria at the last available assessment (51/81), day 64 (51/62), day 183 (16/81), day 302 (4/81), day 394 (4/81) and day 578 (4/81). Four patients (out of 24) who received sham control in ENDEAR and then nusinersen in SHINE met the HINE-2 response criteria at day 302 (but not at any other time point) and no patients who received only sham in ENDEAR met the criteria at any timepoint (Supplementary Appendix 1,[3] Figure 2C). Similarly, a decreasing proportion of patients who received nusinersen in ENDEAR and SHINE met the CHOP INTEND score response criteria at the last available assessment (55/81), day 64 (33/81), day 183 (14/81), day 302 (4/81), day 394 (3/81) and day 818 (1/81). Eleven patients (out of 24) who received sham control in ENDEAR and then nusinersen in SHINE met the CHOP INTEND response criteria at the last available assessment, 10 (out of 24) met the criteria at day 183 and one (out of 24) met the criteria at day 302 (but not at any other time point). One patient

(out of 41) who received only sham in ENDEAR met the CHOP INTEND response criteria at the last available assessment, and at day 302 (Supplementary Appendix 1,[3] Figure 2D). At the last available assessment, the highest motor milestone achieved among patients who received nusinersen in ENDEAR and SHINE was full head control in 23/81 (28%) patients and independent sitting in 12/81 (15%) patients; no patients had achieved standing unaided or walking independently. The status of the remaining 57% of patients is not reported in the company's supplementary appendix.

The median time to death or permanent ventilation was 73.0 weeks (95% CI 36.3 to "not available") in patients treated with nusinersen in ENDEAR and SHINE, and 22.6 weeks (95% CI 13.6 to 31.3) in patients who received either sham control in ENDEAR only, or sham control in ENDEAR and nusinersen in SHINE (the ERG is unclear regarding the relevance of combining patients on sham control and nusinersen). Twelve of the 24 patients who received sham control in ENDEAR and nusinersen in SHINE were alive without permanent ventilation at baseline in SHINE, seven of whom were alive without permanent ventilation at the time of data cut-off.

The supplementary appendix states that the safety findings are consistent with those previously reported for nusinersen, with no further details provided.

2.3 ERG comments on the additional evidence from ENDEAR and SHINE

- Interim results from SHINE were not presented in the CS;[5] however, all the results reported in the company's supplementary appendix were provided within the company's clarification response,[6] and the ERG has previously commented on these in the ERG report[7] (page 46).
- The follow-up time points for the outcomes presented are a little clearer; however, there are only longer-term data (2 to 2.5 years) for a very small number of patients, and the timepoints across treatment arms are not comparable in the SHINE data.
- Data from SHINE indicate that a greater proportion of patients met HINE-2 and CHOP INTEND response criteria for the first time at earlier timepoints, although a small number of patients receiving nusinersen in SHINE (including some who had previously received sham control treatment in ENDEAR) achieved first response at later assessment timepoints, including as late as day 818. This suggests that it may take some patients a considerable amount of time to respond to nusinersen.
- The number and duration of hospitalisations were not included as an outcome in the NICE scope;[8] however, the ERG considers that these represent clinically relevant outcomes.
- Data from SHINE suggest that motor milestones of full head control and independent sitting were improved upon or maintained: 22% infants in the nusinersen group in ENDEAR had full head control, compared with 28% of those who received nusinersen in ENDEAR and SHINE. Likewise, 8% infants in the nusinersen group in ENDEAR were able to sit independently,

compared with 15% of those who received nusinersen in ENDEAR and SHINE. Data from ENDEAR reported in the CS[5] suggested that 10% of infants in the nusinersen group were able to roll over, and 1% were able to stand; data from SHINE report that no patients were yet able to stand unaided, with the proportion able to roll over not reported.

3.1 Company's updated health economic models

3.1.1 Amendments to the company's model structures

As part of their ACD response,[2] the company provided new models for the early and later onset SMA populations. The ERG notes that these models adopt a different structural approach to the company's original base case models.[5] The original base case models assumed that, during any given cycle in the extrapolation period, nusinersen-treated patients could not lose motor milestones (they could only improve or stay in the same health state), whilst BSC patients could not gain milestones (they could only worsen or stay in the same state). The company's original models contained some functionality which allowed different structural assumptions to be made, such that a proportion of nusinersen-treated patients could be assumed to plateau or worsen, whilst the remainder continue to transition to improved health states. This functionality increased the complexity of the model programming and did not form part of the company's original base case.[5] As a consequence of these two factors, the ERG did not verify or critique this alternative formulation of the company's models.

The new models provided in response to the ACD adopt the structural approach described above (i.e. subgrouping of patients who improve, plateau or worsen). As the company notes in Supplementary Appendix 2 of their ACD response,[4] [redacted]

The ERG notes that within the company's new models, the individual calculations which implement the Markov traces are considerably simpler than those used in the original models (see formulae shown in ERG report,[7] Box 2). However, the company's new models each use seven sub-models which: (a) track how many patients enter the sub-model at each timepoint; (b) adjust the cohort according to mortality risks and (c) apply matrix multiplication to determine health state occupancy in the subsequent cycle. In addition, there is some mixing between the sub-models to account for patients discontinuing treatment as a consequence of losing efficacy and/or undergoing scoliosis surgery, hence the models are further complicated by the need to track incident and prevalent cohorts within the sub-models. As such, the new models are simpler than the original models in some respects, but more complex in others; this complexity led to difficulties for the ERG in checking the models and in understanding the underlying logic. Based on a rebuild of slightly simplified versions of the company's new models (discussed in Section 3.2) and additional correspondence with the company, the seven sub-models are outlined broadly in Table 1 and the subsequent text.

Table 1: Summary of company's new sub-model structure for early and later onset models

Sub-model number	Sub-model description	How patients enter this sub-model	Transition matrix and mortality risks applied in sub-model	How patients leave this sub-model
1	No scoliosis surgery, on treatment ("improvers")	All patients except those with no milestones at the end of the observed period are assumed to start in this sub-model at the beginning of the extrapolation period	"Improvers" matrix, nusinersen mortality risk	(a) 1% patients assumed to become "worseners" during each cycle, move to sub-model 3 (b) Scoliosis surgery, on treatment (stay "improver"), move to sub-model 5 (c) Scoliosis surgery, discontinue (become "worsener"), move to sub-model 4 or sub-model 7 (c) Death
2	No scoliosis surgery, on treatment ("plateauers")	Redundant – patients never enter sub-model 2	"Plateauers" matrix i.e. probability=1 on matrix diagonal, nusinersen mortality risk	Redundant – patients never enter sub-model 2
3	No scoliosis surgery, discontinue ("worseners")	1% of all nusinersen "improvers" (each cycle) from sub-model 1	BSC ("worseners") matrix, BSC mortality risk	Death
4	Scoliosis surgery, discontinue	From sub-model 1	BSC ("worseners") matrix, BSC mortality risk	Death
5	Scoliosis surgery, on treatment ("improvers")	A proportion of patients move here from sub-model 1 at the time of scoliosis surgery (dependent on ambulatory status)	"Improvers" matrix, nusinersen mortality risk	(a) 1% patients assumed to become "worseners" during each cycle, move to sub-model 7 (b) death
6	Scoliosis surgery, on treatment ("plateauers")	Redundant – patients never enter sub-model 6	"Plateauers" matrix i.e. probability=1 on matrix diagonal, nusinersen mortality risk	Redundant – patients never enter sub-model 6
7	Scoliosis surgery, discontinue ("worseners")	1% of all post-surgery nusinersen "improvers" (each cycle) from sub-model 1 or sub-model 5	BSC ("worseners") matrix, BSC mortality risk	Death

During the extrapolation period, the models assume that patients who achieved no milestones (the worst health state in both models) in the ENDEAR/CHERISH trial periods will subsequently remain in that state until death, hence they never gain/regain any milestones. Patients in any other health state which is better than the no milestones state at the end of the observed period are assumed to progress according to a trajectory of improvement (sub-model 1 – "improvers" i.e. patients cannot lose milestones within this sub-model). During each cycle, 1% of patients who are "improvers" (sub-model 1) are assumed to simultaneously become "worseners" and discontinue nusinersen and move to sub-model 3; these patients follow a general trajectory of worsening and cannot subsequently regain milestones. No patients are assumed to plateau, hence sub-model 2 is redundant in the company's base case models. For "worseners", (sub-model 3), the models track incident and prevalent patients. When the model timepoint exceeds the time at which scoliosis surgery is assumed to apply (12 years for non-ambulant states or 15 years for ambulant patients), a proportion of patients transition to sub-models 4-7 (hence the model assumes further mixing between sub-models). As the models do not include a cost, health impact or prognosis impact associated with scoliosis surgery, the ERG believes that the implementation of sub-models 4-7 is equivalent to simply raising the nusinersen worsening and discontinuation probability for "improvers" (sub-model 1) at the time of scoliosis surgery (i.e. a greater proportion of "improvers" become "worseners" at that particular timepoint). Health state transitions for patients who are still receiving nusinersen are governed by the "improvers" (nusinersen) matrix, whilst transitions for patients who have discontinued treatment are governed by the "worseners" (BSC) matrix; these matrices are the same as those applied in the company's original model. Mortality risk for patients who are still receiving nusinersen is determined by the nusinersen group survival model; mortality risk for patients who have worsened and discontinued is governed by the BSC group survival model.

The company's new models apply the following survival assumptions:

- Early onset population – Weibull model fitted to ENDEAR data with tapered hazard ratio (HR) over 60 months in the nusinersen group
- Later onset population – flexible spline-based Weibull (2 knots) with subsequently uplifted general population mortality rates.

3.1.2 Summary of amendments to the company's model parameters

The company's new early and later onset models include a number of parameters which have been changed. Overall, the ERG considers that most of these amendments address concerns raised by the ERG and the Appraisal Committee regarding the original base case models.[1, 7] The main parameters which have been amended are shown in Table 2.

Table 2: Summary of company's amendments to the model parameters in response to the ACD

Model component / parameter	Company's original base case models	ERG-preferred approach / comment	Company's new base case models
Initial health state distribution	Initial distribution based on CHOP INTEND/HFMSE score in each treatment group	Same initial distribution should be applied in each group	As per ERG critique
Cost of death	Costs of death included only in early onset model	Cost of death should be included in early and later onset models	As per ERG critique
Patient utilities	Based on CHERISH PedsQL mapped to EQ-5D utilities using algorithm reported by Khan *et al*[9]	Lloyd *et al* EQ-5D vignette study[10] used in ERG-preferred analysis; estimates from ERG's clinical advisors used in exploratory analyses	Based on Lloyd *et al* EQ-5D vignette study[10]
Caregiver utilities	Based on a set of assumptions regarding general population utility and patient utility decrements between states	Estimates by SMA type from Bastida *et al*[11] linked to health states reflective of those SMA types (as reported, without adjustment).	Assumes best health state is associated with general population utility; worst state is associated with mean caregiver utility in Bastida *et al*;[11] equal difference in utility assumed between adjacent states. The only exception is that the same caregiver utility is applied for the 'stands unaided' and 'walks unaided' states in the later onset SMA model (not explained in appendix[4]).
Number of caregivers	1 caregiver	Not commented on	2 caregivers
Costs by health state	Sourced from cross-sectional study reported by Bastida *et al*[11]	ERG commented that estimates from Bastida *et al*[11] appear low and may be time-/age-dependent	Based on real-world evidence (RWE) study conducted by company in 2017
Early onset SMA mortality risk	Based on 1-knot spline fitted to ENDEAR data, subsequent use of exponential model fitted to Gregoretti *et al*,[12] 2-knot spline fitted to Zerres *et al*[13] and HR-adjusted general population mortality. Mortality risk multiplier applied to better health states	The ERG's clinical advisors noted that the company's survival projections were highly uncertain and appeared highly optimistic. Simpler approaches may be appropriate. Reported outcomes from Gregoretti *et al*[12] (early onset model) are poorer than would be expected. State-dependent mortality risk adjustment factors are not based on empirical evidence. Alternative mortality	Weibull model with HR tapered over 60 months, followed by uplifted general population mortality. Smaller survival gain than company's original base case model.

Model component / parameter	Company's original base case models	ERG-preferred approach / comment	Company's new base case models
Later onset SMA mortality risk	No mortality in observed period, 2-knot spline fitted to Zerres,[13] uplifted/unadjusted general population thereafter. Mortality risk multiplier applied to better health states	risk multipliers explored in ERG exploratory analyses.	2-knot spline followed by uplifted general population mortality. No incremental survival gain for nusinersen assumed in company's new base case model.
Data used to determine CHOP INTEND/HFMSE thresholds for transitions in extrapolation period	"Each arm" data used (different thresholds for each treatment group)	"Both arm" data preferred (same thresholds for both treatment groups)	As per ERG critique
Probability of undergoing scoliosis surgery in early onset model	1%	Not commented on	43%
Progression trajectory for nusinersen-treated patients	In the extrapolation period, surviving nusinersen-treated patients assumed never to lose milestones	Some proportion of patients are likely to lose milestones or plateau. No patients reached the best health states in ENDEAR or CHERISH. Less optimistic matrices (allowing worsening) applied in exploratory analyses.	1% of patients assumed to lose efficacy and discontinue during each model cycle; these patients never regain milestones. Patients remaining on treatment continue to gain milestones.

3.1.3 Key cost-effectiveness results presented in the Supplementary Appendix 2 of the company's ACD response

Early onset population model results

Table 3 summarises the results of the company's new early onset model base case and subgroup analyses (based on disease duration). Based on the deterministic version of the model, the base case ICER including only patient health gains is estimated to be [redacted] per quality-adjusted life year (QALY) gained. Across three sets of analyses using the probabilistic version of the model (conducted by the ERG using different random numbers in each analysis), the ICER was estimated to be between [redacted] and [redacted] per QALY gained. When caregiver health impacts are also included in the model, the deterministic ICER is reduced to [redacted] per QALY gained. The ERG was unable to generate probabilistic ICERs which include caregiver health impacts using the model provided. Across all of the company's scenario analyses, the lowest ICER (including caregiver health impacts) is [redacted] per QALY gained (≤12 weeks disease duration subgroup, see Table 3 footnotes), whilst the highest ICER is [redacted] per QALY gained (>12 weeks disease duration subgroup, see Table 3 footnotes).[4]

Compared with the company's original early onset base case model,[5] the key drivers of the higher ICER in the new early onset model are: (i) the use of less favourable mortality assumptions; (ii) the use of the vignette study for patient utilities, and (iii) the use of the real-world evidence (RWE) survey to inform health state costs.

Table 3: Company's early onset model results, including commercial offer (generated by the ERG)

Option	Absolute			Incremental				
	QALYs (patient)	QALYs (patient +carer)	Cost	QALYs (patient)	QALYs (patient + carer)	Cost	ICER (patient)	ICER (patient+ carer)
Company's base case								
Nusinersen	0.57	-0.96	[redacted]	1.05	1.37	[redacted]	[redacted]	[redacted]
BSC	-0.48	-2.34	£176,108	-	-	-	-	-
≤12 weeks disease duration*								
Nusinersen	1.19	0.00	[redacted]	1.68	2.37	[redacted]	[redacted]	[redacted]
BSC	-0.49	-2.37	£176,420	-	-	-	-	-
>12 weeks disease duration*								
Nusinersen	0.10	-1.76	[redacted]	0.57	0.55	[redacted]	[redacted]	[redacted]
BSC	-0.47	-2.31	£175,829	-	-	-	-	-

** The disease duration subgroup analyses presented in Supplementary Appendix 2 of the company's ACD response appear to be slightly incorrect as the mean CHOP INTEND scores reflect those for the ITT population rather than the subgroup. The corrected values are presented in Table 3.*

Later onset population model results

Table 4 summarises the results of the company's new later onset model base case and subgroup analyses (based on disease duration). Based on the deterministic version of the model, the base case ICER including only patient health gains is estimated to be [redacted] per QALY gained. Across three sets of analyses using the probabilistic version of the model (conducted by the ERG using different random numbers in each analysis), the probabilistic ICER was consistently similar to the deterministic ICER (~[redacted] per QALY gained). When caregiver health impacts are also included, the deterministic ICER is reduced to [redacted] per QALY gained; the ERG's probabilistic analyses produced higher ICERs of approximately [redacted] per QALY gained. Across all of the company's scenario analyses, the lowest ICER (including caregiver health impacts) is [redacted] per QALY gained (<25 months disease duration subgroup, see Table 4 footnotes), whilst the highest ICER presented is [redacted] per QALY gained (patient utilities generated from mapping PedsQL to EQ-5D; not shown in Table 4).

Compared with the company's original later onset base case model,[5] the key drivers of the lower ICERs in the later onset population are: (i) the commercial access agreement; (ii) the use of the vignette study for patient utilities;[10] (iii) the new caregiver QALY loss assumptions, including an increase in the number of caregivers, and (iv) the use of the 2017 RWE survey to inform health state costs.

Table 4: Company's later onset model results, including commercial offer (generated by the ERG)

Scenario	Absolute			Incremental				
	QALYs (patient)	QALYs (patient +carer)	Cost	QALYs (patient)	QALYs (patient + carer)	Cost	ICER (patient)	ICER (patient +carer)
Company's base case								
Nusinersen	5.83	-3.56	[redacted]	4.74	10.74	[redacted]	[redacted]	[redacted]
BSC	1.09	-14.30	£1,074,004	-	-	-	-	-
<25 months disease duration*								
Nusinersen	8.07	1.67	[redacted]	7.08	16.49	[redacted]	[redacted]	[redacted]
BSC	0.99	-14.82	£1,077,871	-	-	-	-	-
≥25 months disease duration*								
Nusinersen	5.63	-4.38	[redacted]	3.46	7.23	[redacted]	[redacted]	[redacted]
BSC	2.17	-11.62	£1,025,580	-	-	-	-	-

** The disease duration subgroup analyses presented in Supplementary Appendix 2 of the company's ACD response appear to be slightly incorrect as the mean HFMSE scores reflect those for the ITT population rather than the subgroup. The corrected values are presented in Table 4.*

3.2 Model verification undertaken by the ERG

3.2.1 Verification and critique of company's new model structure

The company's new models adopt a different programming approach and employ different structural assumptions compared with the original base case models. As such, the ERG considered it important to verify how the company's new models operate and to confirm that the commercial access agreement had been appropriately incorporated into the new models. Owing to their complexity, the ERG attempted to verify the new models using three different approaches:

- *Verification approach 1:* Determining whether the new models, modified to reflect the company's original base case assumptions, generate results which are the same as the company's original base case models.
- *Verification approach 2:* Double-programming the deterministic versions of the company's new models to ensure that both models have been implemented correctly.
- *Verification approach 3:* Applying logical tests to ensure that the models behave according to prior expectations.

Verification approach 1 – comparison of results new and original base case models

Table 5 presents a comparison of results generated using the company's new models including the original base case structure and assumptions versus those generated using the company's original base case models. As shown in the table, the new models generate results which are similar, but not identical to the results from the original models. The same issue was highlighted by the company.[4] Correspondence between the ERG and the company suggests that these differences are a consequence of using different approaches to estimate health outcomes and costs for patients who undergo scoliosis surgery. The ERG cannot verify this to be accurate, but notes that the discrepancy between the models is smaller in the early onset model and this population is assumed to have a lower lifetime probability of undergoing scoliosis surgery compared with the later onset population. The ERG does not have major concerns regarding these discrepancies. However, the ERG notes that this is not a particularly meaningful validation test, as both models reflect the original model structure and therefore do not incorporate the company's new structural assumptions (four of the seven new sub-models are not used in this analysis).

Table 5: Comparison of results from company's original base case models and company's new models using company's original assumptions and structure (no worsening for nusinersen-treated patients), excludes commercial access agreement

Scenario	Absolute			Incremental				
	QALYs (patient)	QALYs (patient + carer)	Cost	QALYs (patient)	QALYs (patient + carer)	Cost	ICER (patient)	ICER (patient+ carer)
Company's original early onset model								
Nusinersen	7.86	7.61	£2,258,852	5.37	5.44	£2,187,311	**£407,605**	**£402,361**
BSC	2.49	2.17	£71,540	-	-	-	-	-
Company's new early onset model with original base case model assumptions								
Nusinersen	7.83	7.58	£2,260,654	5.34	5.41	£2,189,113	**£409,981**	**£404,708**
BSC	2.49	2.17	£71,540	-	-	-	-	-
Company's original later onset model								
Nusinersen	16.88	15.66	£3,148,754	2.37	3.30	£2,964,442	**£1,252,991**	**£898,164**
BSC	14.52	12.36	£184,312	-	-	-	-	-
Company's new later onset model with original base case model assumptions								
Nusinersen	16.76	15.50	£3,153,296	2.24	3.14	£2,968,984	**£1,325,758**	**£945,696**
BSC	14.52	12.36	£184,312	-	-	-	-	-

Verification approach 2 – model rebuild

As noted in Section 3.1, the ERG had some concerns regarding the reliability of the new model results as the programming approaches used within the new models as both the new and original models are complex, albeit in different ways. In order to understand how the new models operate and to assess their underlying logic, the ERG rebuilt the deterministic versions of the company's early onset and later onset models. This exercise was undertaken with the intention of ensuring that the replicated results are not significantly different to those presented by the company. Based on these double-programmed models, the ERG was able to generate results which are broadly similar to those generated by the company (results not shown). As such, the ERG is satisfied that the ICERs generated using the company's new models are not likely to be subject to major errors.

On the basis of this double-programming process, the ERG makes the following observations:

- The company's new models assume that a proportion of nusinersen-treated patients will worsen (lose milestones) during the extrapolation period. All of these patients are assumed to discontinue at that point. The ERG considers this assumption to be more reasonable than the assumptions made within the company's original models. However, it is perhaps more plausible that some patients who worsen whilst receiving nusinersen might subsequently recover and gain benefit from continued treatment. This is not captured in the structure of the company's new models; [redacted] This is a structural limitation of the company's new models – the company's model does not reflect the commercial offer made by the company. [redacted]
- From the beginning of the extrapolation period, all nusinersen-treated patients who have achieved any milestones are assumed to be "improvers", with the exception of 1% of patients who are assumed to lose benefit and discontinue during each cycle. There is no evidence to support this discontinuation rate.
- The company's new models assume that patients who are defined as "worseners" will never regain any milestones (including all BSC-treated patients). Within the ENDEAR and CHERISH trials, a proportion of patients in the sham groups improved between assessments. The ERG believes that this assumption may bias in favour of nusinersen, at least for some patients with later onset disease (e.g. those with Type III SMA, whereby the maximal expected motor milestone is walking[14]).
- Whilst the company's ACD response suggests that the new model allows patients to plateau, under the new base case assumptions, no patient ever enters these sub-models. Instead, all

patients who lose treatment benefit are assumed to worsen (and discontinue). This means that sub-model 2 and sub-model 6 (see Table 1) are redundant and add unnecessary complexity.

- Within the early onset model, more than 96% of patients are assumed to have died before they reach 12 years of age. This means that scoliosis surgery has a negligible impact on the ICER for nusinersen, [redacted] As such, sub-models 4, 5, 6, and 7 have almost no influence on the model results and are largely unnecessary in the early onset model. Scoliosis surgery does however have a greater impact in the company's later onset model. As detailed in Section 3.1.1, the ERG believes that these sub-models could have been avoided altogether by applying a higher discontinuation probability at the timepoints at which scoliosis surgery is assumed to apply; this would have resulted in a considerably simpler model structure.

Verification approach 3 –testing model behaviour is consistent with prior expectations

A number of verification tests were used to determine whether the behaviour of the company's new models is consistent with prior expectations (see Table 6). It should be noted that the tests explored by the ERG do not represent an exhaustive list; whilst they may help to identify symptoms of model errors, they do not guarantee that the company's models are error-free. One discrepancy was identified whereby if the per-cycle probability of discontinuation and the probability of undergoing scoliosis surgery were both set equal to 1.0, surviving patients should, but do not, enter the post-scoliosis surgery states; instead, patients remain in sub-model 3. Given that all patients have discontinued treatment, the ICER should be unaffected. On the basis of these tests, the ERG is broadly satisfied that the company's new models operate as expected and that the commercial access agreement has been applied as intended; however, it should be borne in mind that this does not fully reflect the commercial offer made by the company [redacted]

Table 6: Summary of black-box tests applied to the model

Test	Expected effect	ERG assessment - early onset model	ERG assessment – later onset model
[redacted]	[redacted]	Model behaves as expected	Model behaves as expected
[redacted]	[redacted]	Model behaves as expected	Model behaves as expected
[redacted]	[redacted]	Model behaves as expected	Model behaves as expected

Test	Expected effect	ERG assessment - early onset model	ERG assessment – later onset model
4. Set scoliosis surgery probability equal to zero	No patient should enter sub-models 4, 5, 6 or 7 (post-scoliosis surgery sub-models)	Model behaves as expected	Model behaves as expected
5. Set discontinuation probability equal to 1.0	All patients should immediately leave sub-model 1	Model behaves as expected	Model behaves as expected
6. Set discontinuation probability equal to zero (including those with no milestones) and scoliosis surgery probability equal to zero	No patient should enter sub-models 2, 3, 4, 5, 6 or 7 (all patients remain "improvers" until death)	Model behaves as expected	Model behaves as expected
7. Set discontinuation probability equal to one (including those with no milestones) and scoliosis surgery probability equal to one	No patient should enter sub-models 1 or 2, some should move to post-scoliosis surgery sub-models	No patient enters sub-model 1. However, no patient ever moves to post-scoliosis surgery states. This appears to be incorrect but may not be important as patients have already discontinued nusinersen.	Model behaves as expected

3.3 ERG commentary on company's amended model parameters

(i) Initial distribution, both arms extrapolation, end of life cost

The company's amendments to the initial health state distribution, the inclusion of end of life costs in both the early and later onset models, and the use of data from both trial arms to determine thresholds for changes in CHOP INTEND and HFMSE are in line with the ERG's critique.[7]

(ii) Changes to survival modelling

(a) Early onset model

Within the company's new early onset model, survival extrapolations are based on a Weibull model, fitted jointly to observed data from both treatment groups (hence assuming proportional hazards) of ENDEAR. This amendment was made following the ERG's advice that a "*simpler approach based on extrapolating parametric models fitted to observed trial data may have been both more informative and more transparent than the approach adopted in the original submission*".[7] The company states that the Weibull is the only model that gives plausible long-term predictions.[4]

Fitted survival curves are provided in Supplementary Appendix 2 of the company's ACD response[4] (Figure 19). The company's base case uses these fitted Weibull probabilities, but applies an additional

tapering of the HR over a period of 60 months; this HR shifts the nusinersen curve towards the placebo baseline curve, thereby reducing incremental survival gains. The company explored this assumption in sensitivity analyses, whereby the HR is tapered over 120 months. Unlike the company's original model, the company's new base case does not apply a mortality adjustment to nusinersen-treated patients in the better health states; however, this is explored in sensitivity analyses.

With respect to this approach, the ERG notes the following:

- The company's amended approach is indeed simpler and more transparent than the method applied in the original base case model.[5] However, the company have not demonstrated that other parametric survival models provide unrealistic extrapolations, nor has the plausibility of the Weibull model been demonstrated.
- The parametric models were fitted jointly to both treatment groups, thereby assuming proportional hazards and a constant HR. This did not impact the original model given that the survival extrapolations were largely driven by other data sources; however, this does affect the company's new model. If the company does not believe that the assumption of proportional hazards holds for the entire time horizon, then parametric models should be fitted separately to both trial arms, rather than using a combined model that assumes proportional hazards. Assuming proportional hazards and then tapering mortality risk in one group using an HR, are not consistent approaches.
- With respect to the estimated lifetime survival benefit of nusinersen versus BSC, this reflects a more conservative approach than the company's original base case model (company's original model = 9.12 additional undiscounted life years gained (LYG); company's new model = 1.66 additional undiscounted LYG).

(b) Later onset model

Within the later onset model, the mortality adjustment factor has been removed, hence survival is assumed to be equal for the nusinersen and BSC groups. Compared with the company's original later onset model, this represents an unfavourable assumption; however, the ERG notes that this change does not have a substantial impact on the ICER.

Overall, the ERG notes that the company's new survival assumptions in both models are more conservative than those employed in the original base case models. The true long-term survival benefit for patients treated with nusinersen remains highly uncertain in patients with early onset SMA and patients with later onset SMA.

(iii) Patient and caregiver utilities

The company's new base case models apply patient utilities based on the vignette study reported by Lloyd *et al*.[10] As noted in the ERG report,[7] none of the available sources for patient utilities are ideal; the Lloyd *et al* study was selected for inclusion in the ERG-preferred analysis as this broadly aligned with the health states used in the company's models and health states were valued using the EQ-5D.[7] The ERG notes that whilst the (non-preference-based) estimates of HRQoL provided by the clinical advisors to the ERG may have greater face validity than any of the empirical estimates available, these are not utility values; these estimates have been included in the company's sensitivity analyses.[4]

The ERG notes that there are two main changes with respect to the caregiver health impacts included in the company's new models:

- Supplementary Appendix 2 of the company's ACD response[4] states that changes in caregiver utility between adjacent patient health states are now assumed to be equal and the minimum caregiver utility has been amended to reflect the mean caregiver utility value reported by Bastida *et al.*[11] The ERG notes that within the new later onset model, the company has actually assumed that caregiver utility is equal for the two best health states; it is unclear whether this was intended.
- The company's original models included QALY impacts for a single caregiver; the company's new models include QALY impacts for two caregivers, thus doubling the QALY losses assumed for carers.

The ERG does not necessarily believe that the company's new caregiver disutility calculations are unreasonable, but notes that they are largely based on assumptions due to a lack of evidence relating patient health states to caregiver utility. The only available estimates which relate to SMA type (and potentially, milestones associated with SMA type) are reported by Bastida *et al*;[11] however, the NICE ACD[1] states that these values were considered to lack face validity. Further, whilst it might be reasonable to include health losses for more than one caregiver, the ERG notes that including this assumption has a significant impact on the ICER for nusinersen. In particular, within the company's new later onset model, caregivers gain more incremental health from nusinersen than patients. The ERG believes that there may be conceptual issues in the interpretation of an economic analysis in which the patient taking the drug is not the main contributor to the overall incremental health gain. These issues should be borne in mind when interpreting the company's ICERs which include caregiver impacts.

(iv) Health state costs by SMA type

The company's new models include different estimates of costs associated with health states. Within the company's original models, costs by health state were based on the cross-sectional study reported by Bastida *et al*.[11] The ERG report[7] commented that these costs appear low, particularly with respect to

those associated with health states consistent with milestones achieved by patients with Type I and II SMA. Within the company's new models, health state costs are based on an RWE survey involving paediatric neurological consultants representing nine UK centres (cited but not used in the CS,[5] see Table 7).

Table 7: Comparison of annual costs from Bastida *et al* (company's original model) and 2017 RWE survey (company's new model)*

SMA type	Bastida *et al*[11]	2017 RWE survey[4]
SMA I	[redacted]	£77,968
SMA II	[redacted]	£55,185
SMA III	[redacted]	£20,229

** Assumed relationship between SMA type and model health states previously reported in ERG report Table 48*

The ERG notes the following regarding the company's new cost estimates:

- The costs from the survey are considerably higher than the estimates from Bastida *et al*.[11]
- The RWE survey data are unpublished and the methods used have not been presented in detail.
- The use of costs from the RWE survey reduce the ICER in the later onset population, but increase the ICER in the early onset population.
- One of the clinical advisors to the ERG believed that the RWE survey costs were likely to be more appropriate than the estimates from Bastida *et al*.[11] The second advisor was unsure.
- As noted in the ERG report,[7] the costs of care are likely to be age-dependent. This is not accounted for in the company's models.

(v) Probability of undergoing scoliosis surgery

The company's new early onset model assumes that 43% of patients will undergo scoliosis surgery (the same proportion applied in the later onset model). This is considerably higher than the value used in the company's original base case model (probability = 1%). However, the proportion of early onset patients who are alive at the time of scoliosis surgery is low. Consequently, this parameter has a negligible impact on the ICER.

3.2.3 Additional ERG comments

The company's ACD response[2] states that [redacted]. The ERG does not consider this to reflect a robust approach to decision-making and notes that there is no evidence to suggest that the cost-effectiveness of nusinersen in the early onset population should be similar to or lower than that for the later onset population.

Instead, the ERG believes that it is more appropriate to attempt to quantify the most plausible ICER for nusinersen within each population based on the available evidence.

With the exception of the company's new caregiver assumptions, the ERG believes that the company has presented ICERs for nusinersen which generally reflect a more appropriate and potentially unfavourable set of assumptions compared with those included in the original models. It is important to note that some of these changes have a favourable impact on the ICER for one population, but a negative impact on the other. The subsequent section explores the impact of key uncertainties using the company's new base case models, incorporating the impact of the commercial access agreement.

4. Additional analyses undertaken by the ERG

The ERG undertook 11 additional exploratory analyses using the company's new base case models, including the commercial access agreement. The following scenarios were undertaken:

- *ERG analysis 1:* Apply company's commercial access agreement using the company's original models [redacted]
- *ERG analysis 2:* Mortality – remove tapering of HR
- *ERG analysis3:* Mortality – apply company's original model mortality assumptions
- *ERG analysis 4:* ERG clinical advisors' HRQoL estimates
- *ERG analysis 5:* Caregiver QALYs – assume 1 caregiver
- *ERG analysis 6:* RWE survey costs halved
- *ERG analysis 7:* Discontinuation probability = 0.5%
- *ERG analysis 8:* Discontinuation probability = 2%
- *ERG analysis 9:* Rate of BSC progression halved
- *ERG analysis 10:* Rate of nusinersen improvement doubled
- *ERG analysis 11:* Most favourable scenario in ITT population analyses applied to shorter disease duration subgroup

Early onset SMA population

Table ***8*** presents the results of the ERG's exploratory analyses within the company's new early onset model. In the ITT population, the lowest ICERs generated from these models relate to the scenario in which the commercial access agreement is crudely applied in the company's original base case model; this analysis suggests ICERs of [redacted] per QALY gained when patient health gains are included, and [redacted] per QALY gained when patient and caregiver health impacts are included. Applying this scenario within the ≤12 weeks disease duration subgroup leads to slightly lower ICERs of [redacted] per

QALY gained (patient health gains only) and [redacted] per QALY gained (patient and carer health impacts). As discussed in the ERG report,[7] these ICERs reflect a highly optimistic scenario.

Table 8: ERG exploratory analyses, early onset model, including commercial access agreement (unless otherwise stated), deterministic model

Scenario	Absolute			Incremental				
	QALYs (patient)	QALYs (patient +carer)	Cost	QALYs (patient)	QALYs (patient +carer)	Cost	ICER (patient)	ICER (patient+ carer)
Company's new base case model with commercial access agreement								
Nusinersen	0.57	-0.96	[redacted]	1.05	1.37	[redacted]	[redacted]	[redacted]
BSC	-0.48	-2.34	£176,108	-	-	-	-	-
ERG analysis 1: Company's original base case model with commercial access agreement								
Nusinersen	7.86	7.61	[redacted]	5.37	5.44	[redacted]	[redacted]	[redacted]
BSC	2.49	2.17	£71,540	-	-	-	-	-
ERG analysis 2: Mortality HR tapering removed								
Nusinersen	1.45	-0.20	[redacted]	1.92	2.13	[redacted]	[redacted]	[redacted]
BSC	-0.48	-2.34	£176,108	-	-	-	-	-
ERG analysis 3: Company's original model mortality assumptions applied to new model								
Nusinersen	2.97	0.75	[redacted]	3.75	4.48	[redacted]	[redacted]	[redacted]
BSC	-0.78	-3.73	£274,206	-	-	-	-	-
ERG analysis 4: ERG clinical advisors' HRQoL estimates								
Nusinersen	1.91	0.38	[redacted]	1.46	1.79	[redacted]	[redacted]	[redacted]
BSC	0.45	-1.41	£176,108	-	-	-	-	-
ERG analysis 5: Assume 1 caregiver								
Nusinersen	0.57	-0.20	[redacted]	1.05	1.21	[redacted]	[redacted]	[redacted]
BSC	-0.48	-1.41	£176,108	-	-	-	-	-
ERG analysis 6: RWE survey costs halved								
Nusinersen	0.57	-0.96	[redacted]	1.05	1.37	[redacted]	[redacted]	[redacted]
BSC	-0.48	-2.34	£93,444	-	-	-	-	-
ERG analysis 7: Discontinuation probability = 0%								
Nusinersen	0.73	-0.69	[redacted]	1.21	1.65	[redacted]	[redacted]	[redacted]
BSC	-0.48	-2.34	£176,108	-	-	-	-	-
ERG analysis 8: Discontinuation probability = 2%								
Nusinersen	0.44	-1.19	[redacted]	0.92	1.14	[redacted]	[redacted]	[redacted]
BSC	-0.48	-2.34	£176,108	-	-	-	-	-
ERG analysis 9: Rate of BSC deterioration halved								
Nusinersen	0.59	-0.92	[redacted]	1.07	1.41	[redacted]	[redacted]	[redacted]
BSC	-0.48	-2.33	£176,108	-	-	-	-	-
ERG analysis 10: Rate of nusinersen improvement doubled								
Nusinersen	0.81	-0.58	[redacted]	1.29	1.75	[redacted]	[redacted]	[redacted]
BSC	-0.48	-2.34	£176,108	-	-	-	-	-
ERG analysis 11: Most favourable scenario (original model scenario) applied in ≤12 weeks disease duration subgroup								
Nusinersen	10.07	9.86	[redacted]	7.72	7.81	[redacted]	[redacted]	[redacted]
BSC	2.35	2.05	£68,582	-	-	-	-	-

Later onset SMA population

Table 9 presents the results of the ERG's exploratory analyses within the company's new later onset model. Of the analyses explored in the ITT population, the lowest ICERs relate to the analysis in which

the rate of HFMSE score improvement for nusinersen-treated patients is doubled; this analysis suggests ICERs of [redacted] per QALY gained when patient health gains are included, and [redacted] per QALY gained when patient and caregiver health impacts are included. Applying this scenario within the <25 months disease duration subgroup leads to ICERs of [redacted] per QALY gained (patient health gains only) and [redacted] per QALY gained (patient and carer health impacts).

Table 9: ERG exploratory analyses, later onset model, including commercial access agreement (unless otherwise stated), deterministic model

Scenario	Absolute			Incremental				
	QALYs (patient)	QALYs (patient + carer)	Cost	QALYs (patient)	QALYs (patient + carer)	Cost	ICER (patient)	ICER (patient+ carer)
Company's new base case model with commercial access agreement								
Nusinersen	5.83	-3.56	[redacted]	4.74	10.74	[redacted]	[redacted]	[redacted]
BSC	1.09	-14.30	£1,074,004	-	-	-	-	-
ERG analysis 1: Company's original base case model with commercial access agreement								
Nusinersen	16.88	15.66	[redacted]	2.37	3.30	[redacted]	[redacted]	[redacted]
BSC	14.52	12.36	£184,312	-	-	-	-	-
ERG analysis 2: Mortality HR tapering removed								
Nusinersen	5.83	-3.56	[redacted]	4.74	10.74	[redacted]	[redacted]	[redacted]
BSC	1.09	-14.30	£1,074,004	-	-	-	-	-
ERG analysis 3: Company's original model mortality assumptions applied to new model								
Nusinersen	6.29	-3.22	[redacted]	5.21	11.08	[redacted]	[redacted]	[redacted]
BSC	1.09	-14.30	£1,074,375	-	-	-	-	-
ERG analysis 4: ERG clinical advisors' HRQoL estimates								
Nusinersen	13.58	4.20	[redacted]	1.74	7.74	[redacted]	[redacted]	[redacted]
BSC	11.85	-3.54	£1,074,004	-	-	-	-	-
ERG analysis 5: Assume 1 caregiver								
Nusinersen	5.83	1.14	[redacted]	4.74	7.74	[redacted]	[redacted]	[redacted]
BSC	1.09	-6.60	£1,074,004	-	-	-	-	-
ERG analysis 6: RWE survey costs halved								
Nusinersen	5.83	-3.56	[redacted]	4.74	10.74	[redacted]	[redacted]	[redacted]
BSC	1.09	-14.30	£539,008	-	-	-	-	-
ERG analysis 7: Discontinuation probability = 0%								
Nusinersen	7.31	-0.70	[redacted]	6.22	13.60	[redacted]	[redacted]	[redacted]
BSC	1.09	-14.30	£1,074,004	-	-	-	-	-
ERG analysis 8: Discontinuation probability = 2%								
Nusinersen	4.93	-5.34	[redacted]	3.84	8.96	[redacted]	[redacted]	[redacted]
BSC	1.09	-14.30	£1,074,004	-	-	-	-	-
ERG analysis 9: Rate of BSC deterioration halved								
Nusinersen	6.30	-2.53	[redacted]	5.06	11.24	[redacted]	[redacted]	[redacted]
BSC	1.23	-13.77	£1,068,173	-	-	-	-	-
ERG analysis 10: Rate of nusinersen improvement doubled								
Nusinersen	6.17	-2.88	[redacted]	5.09	11.42	[redacted]	[redacted]	[redacted]
BSC	1.09	-14.30	£1,074,004	-	-	-	-	-
ERG analysis 11: Most favourable scenario (nusinersen improvement rate doubled) applied in <25 months disease duration subgroup								
Nusinersen	8.21	1.96	[redacted]	7.22	16.78	[redacted]	[redacted]	[redacted]
BSC	0.99	-14.82	£1,077,871	-	-	-	-	-

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BIOGEN

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

[ID1069] Nusinersen (SPINRAZA®) for the treatment of 5q Spinal Muscular Atrophy

Cost-effectiveness model revisions and updated results – addendum 1

Executive Summary

- The innovative and life changing benefit of nusinersen was recognised in UK Prix Galien award where nusinersen won in the orphan medicine category (and nine other Prix Galien awards around the world) including 6 other orphan medicines. Sir Michael Rawlins stated "Clinical studies show powerful evidence of improved survival alongside patients achieving and/or maintaining developmental motor milestones closer to those expected for their age and inconsistent with the progressive decline associated with the natural history of the disease. Spinraza's Prix Galien victory is well deserved and was the unanimous decision of the judging panel". Three members of the panel are also chairs of NICE committees.
- Despite being an orphan medicine nusinersen was studied in a robust and comprehensive clinical development programme. It is the largest programme in SMA (380 patients) encompassing eight high-quality studies, including two phase III randomised double-blind, sham-controlled trials in symptomatic infantile onset and later onset patients with spinal muscular atrophy (SMA), both of which have been published in the NEJM, one of the most prestigious peer-reviewed medical journals.
- Despite the published clinical data there remain challenges in assessing nusinersen within a NICE STA process:
    - Long-term clinical data; due to the proven benefits of nusinersen at interim analysis and the large unmet need for a treatment for SMA patients, the pivotal clinical trials were stopped early on ethical grounds
    - The wide spectrum of SMA as a disease; the natural history, and therefore the nusinersen value proposition, are very different in type I SMA when compared to later onset (type II/III SMA)
    - The acknowledged difficulties in assessing the quality of life in paediatric patient populations
    - Lack of UK specific data on the costs of managing SMA, especially given the rapidly evolving standards of care
    - In the current model nusinersen does not meet cost-effectiveness thresholds at zero cost in type I SMA patients. This is due to the significant positive impact that nusinersen has in extending survival in patients of which most will die in the first few years of life. This extension in life leads to increased NHS care costs and caregiver burden.
- Despite these difficulties Biogen have been successful in reaching agreements in 24 EU countries, including Scotland (see Appendix F). Biogen are grateful for the feedback that NICE have given in helping contextualise committee concerns to enable us to make amendments to the economic modelling to increase confidence in the resulting output.
- Since the last submission, Biogen have:
    - Revised the economic model parameters to capture changes suggested by the ERG
    - Incorporated the available longer-term SHINE data for the infantile onset type I patient population
    - Validated the impact on carers of patients with SMA via a carer survey distributed by the PAGs
    - Validated the clinical and costing assumptions used in the economic model via interviews conducted with clinical experts
    - [redacted]
- The previously proposed starting and stopping criteria drawn up in conjunction with NICE, clinicians and patient advocacy groups remain valid. Biogen reiterate their commitment to data collection particularly to assess the impact on quality of life.
- Biogen have also continued to engage with NHS England regarding their willingness to fund both infantile and later onset patients.

Biogen now call on NICE to recommend nusinersen:

- For later onset (type II/III) SMA patients – the ICER submitted is above the standard NICE willingness to pay threshold of £30,000 but we believe could be found to be plausibly cost effective given the unavoidable uncertainties and uncaptured benefits of nusinersen in this patient population. These uncaptured benefits include:
    - Important benefits to patients of improvements in fine motor function which are neglected in the economic model because the health states are gross motor functions
    - Wider societal perspective including loss of employment and productivity for patients, families and carers
- For infantile onset (type I) SMA patients – given the high costs of managing SMA in this patient population and the significant survival benefit that nusinersen has shown in both the clinical trials and through the EAP, the economic modelling demonstrates that nusinersen would not meet NICE willingness to pay thresholds at zero cost. NHS England have an urgent commissioning policy (reference 170018/P) relating to the Expanded Access Programme (EAP). The EAP, after being open for two years is now shut to new patients. Existing patients continue to receive nusinersen and NHS England have indicated a willingness to consider commissioning nusinersen in this patient population based on a positive NICE recommendation in type II / III SMA patients.

1. Background

This document sets out revisions to the cost-effectiveness model for nusinersen following the NICE appraisal committee meeting on 23rd October 2018. Since the meeting, Biogen have remained in dialogue with NICE on how best to address committee discussions regarding:

- the complexity of the economic model
- the integration of extension study data where available to revise optimistic transition probabilities for nusinersen post trial follow-up (particularly the proportion of patients reaching the best health state)
- validation of outcomes on and off treatment against clinical practice
- further exploration of burden placed on families and caregivers
- simplifying the commercial offer
- reducing the ICERs to within plausible cost-effectiveness ranges.

In response to these discussions, we've undertaken a number of actions including updating the economic model with infantile onset data from SHINE, collaborated with patient advisory groups (PAGs) to better understand the burden of SMA and conducted a series of validation meetings with 4 clinical experts across England.

This document details the output of these activities to accompany the economic model. For model version control the previous submission refers to:

- ***Previous submission version*** - Nusinersen (Spinraza)_NICE_CEM_Early and Later Onset_Final CIC_ACD comments Final_
- ***Revised version*** (in accompaniment to this appendix) - ID1069 Nusinersen (Spinraza)_NICE_Infantile and later onset_CEM_18 Jan 2019_final

2. Cost-effectiveness model revisions

2.1 Infantile Onset (type I SMA)

The model structure for infantile onset remains the same as the previous submission. However due to updates to transition matrices post trial follow-up, all 'sub-models' are now active (different from the previous submission whereby 'plateauing' matrices were not used). Furthermore, the nusinersen arm has been updated with available data from SHINE out to day 818. Clinical validation exercises were conducted using these data.

2.1.1 Survival

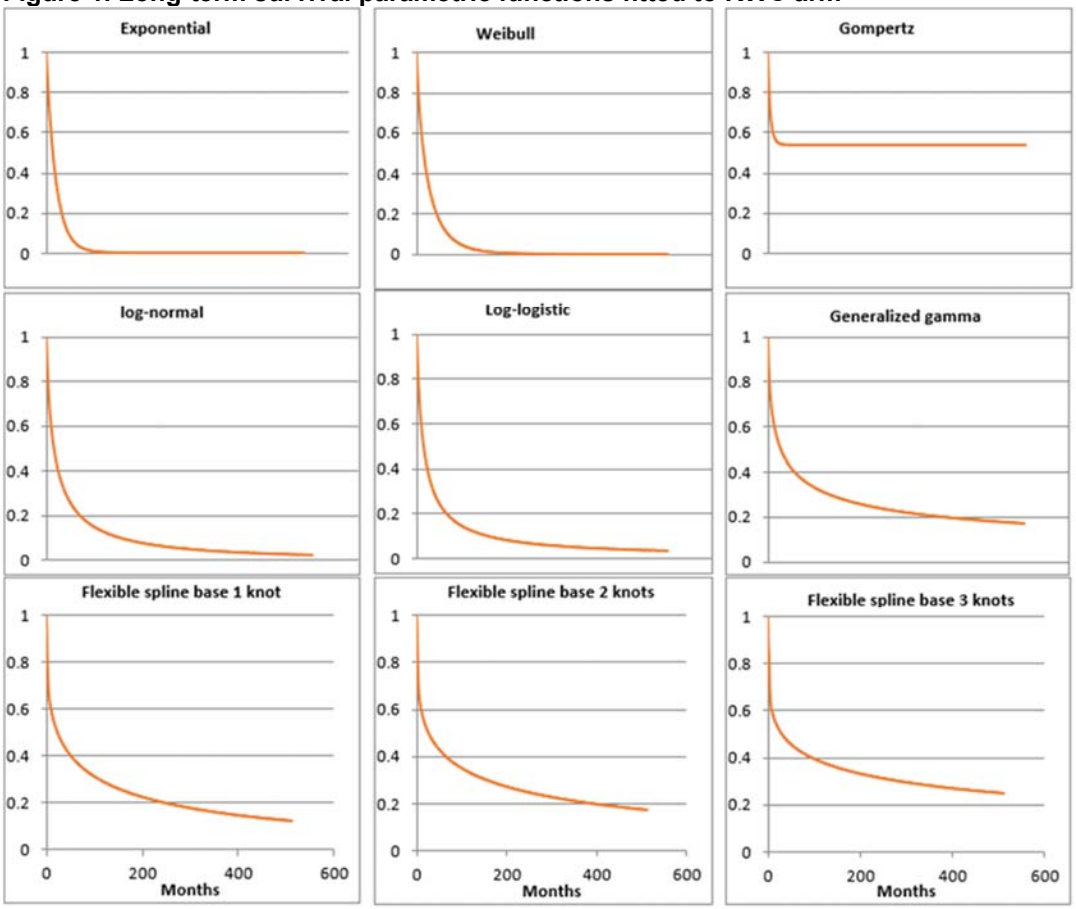
Based on the available data in SHINE (out to day 818), the parametric survival functions were updated in both arms. The functions were fitted to the RWC data observed in ENDEAR only (Due to ethical considerations all patients in the sham control arm in ENDEAR were switched to nusinersen in SHINE. Of these patients, only 2 deaths were observed in SHINE. Due to the limited number of events coupled with the small sample size in SHINE, it was considered reasonable not to conduct a treatment switching analysis to inform survival estimates for the RWC arms). For nusinersen, parametric survival functions were fitted to data observed in ENDEAR + SHINE (must have received nusinersen both studies).

For the RWC arm we used the curves fitted to the ENDEAR data (Figure 1). The parametric functions for the RWC arm were selected based on plausibility of long-term prediction. We included only those functions that predicted less than 20% of survivors at 10 years (natural history data showed estimates at 10 years

between 0% and 10% (Zerres and Rudnik-Schöneborn 1995, Ge et al. 2012, Farrar et al. 2013) [1-3]. Survival estimates greater than 20% under standard of care by 10 years were considered as unlikely by clinical experts.

We included the following functions with plausible long-term predictions: Exponential, Weibull, Log-normal, Log-logistic. We also included the flexible Weibull function with 1 knot as one of the best fitting functions, but it needs to be used along with long term data to produce plausible long-term estimates.

Figure 1. Long-term survival parametric functions fitted to RWC arm



Note: we have used the stratified functions originally fitted to both arms of the ENDEAR data

For the nusinersen arm we fitted parametric functions to the data from ENDEAR and SHINE (Figure 2 and Figure 3).

Figure 2. Parametric curves fitted to the nusinersen arm in ENDEAR+SHINE

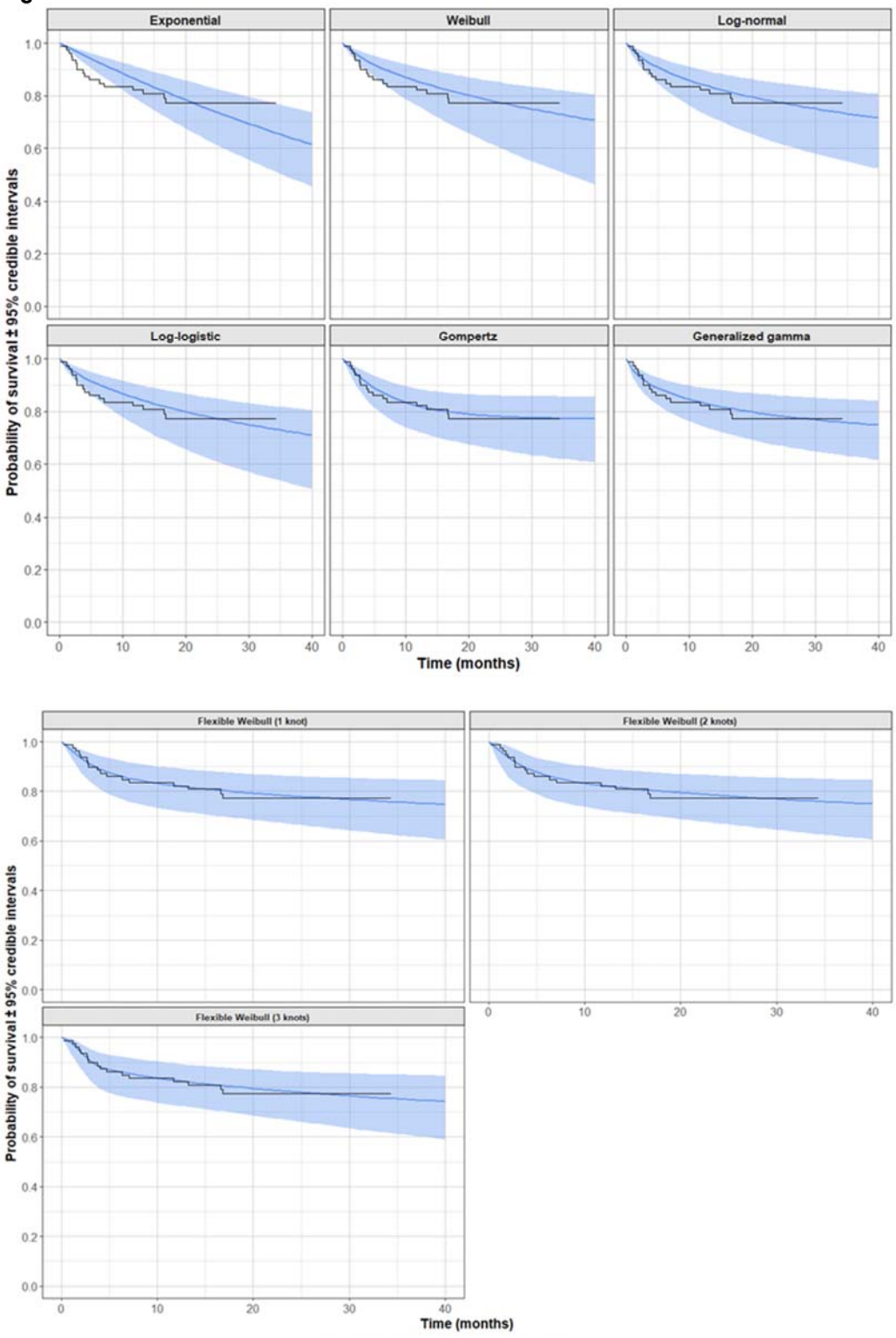
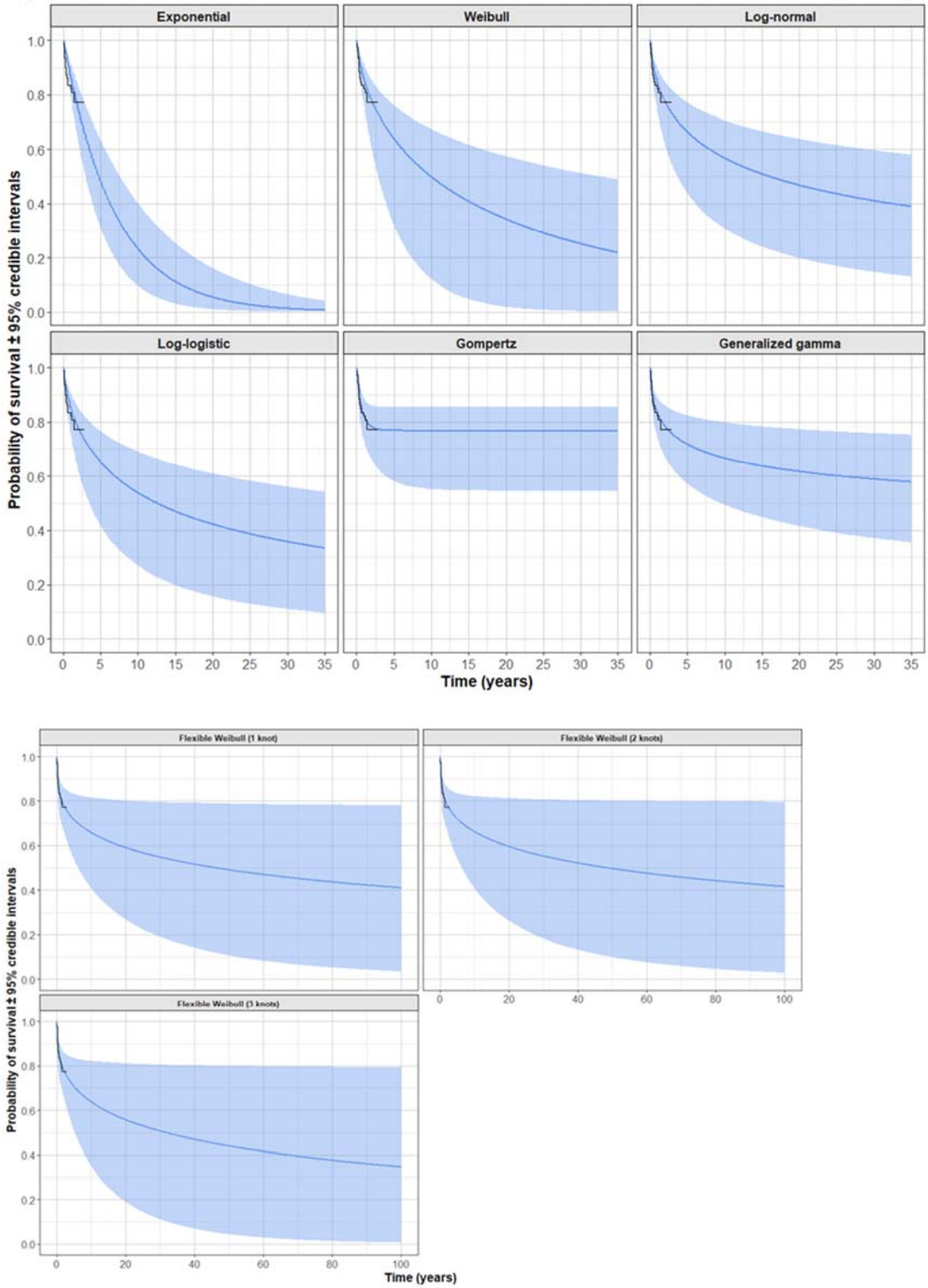


Figure 3. Parametric curves fitted to the nusinersen arm in ENDEAR+SHINE – Long term predictions



We included the same parametric functions selected for the RWC arm, which resulted in the lower long-term predictions. The fit of these functions (Exponential, Weibull, Log-normal, Log-logistic) were among the

worst (visual fit, AIC, BIC, integrate brier score; Figure 4 and Figure 5). The flexible Weibull function with 1 knot showed a good fit, but had a higher long-term survival compared to the others.

Figure 4. AIC and BIC scores

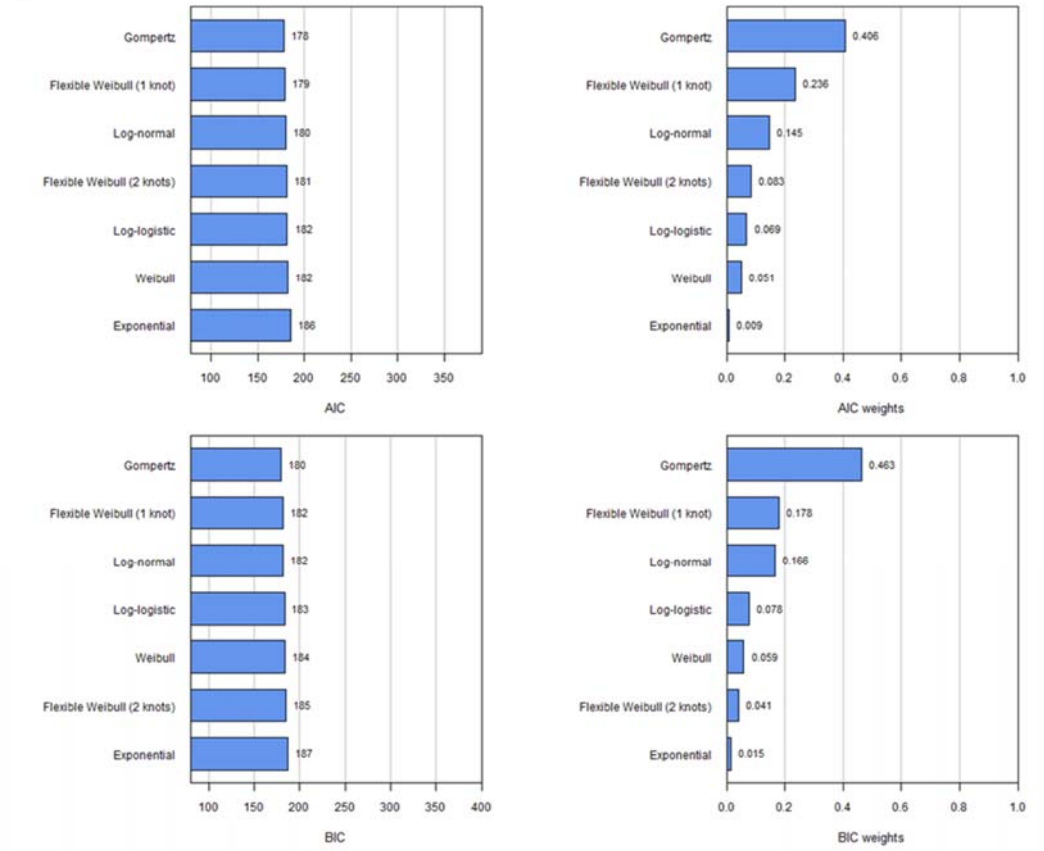
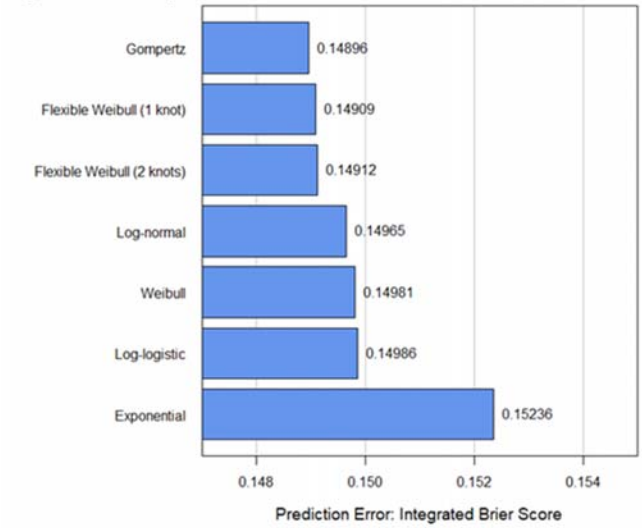


Figure 5. Integrated brier score



With regards to survival predictions, all of the consulted clinical experts stated that the approaches to standards of care (SOC) have changed considerably in the last year(s) and now should follow the guidelines published by Mercuri et al, 2018 and Finkel et al, 2018 [4, 5], despite lack of access to disease modifying therapies. Despite some patients electing for palliative care, there are ethical considerations in more interventional approaches to SOC (non-invasive ventilation, PEG tubes, physiotherapy etc.) ensuring a child is as healthy as possible when a treatment does become available.

Two of the four clinical experts believed that the estimated RWC survival mean of 2.14 life years (undiscounted) was reasonable as of today, although they expected this to increase in future with more interventional approach to SOC. The remaining clinical experts believed this estimate to be marginally optimistic versus historical experience and literature, although they both noted that the long-term survival is significantly influenced by the type of respiratory intervention (e.g. invasive/permanent ventilation vs. non-invasive ventilation) which varies across countries and regionally within the UK. A consensus between clinicians was reached with respect to a maximum of 10-20% of type I patients reaching the first decade of life.

With regards to nusinersen, clinicians believed the estimates provided in the previous submission were overly pessimistic (mean undiscounted survival 4.02 years). These estimates were based on ENDEAR only, using the Weibull function fitted to both arms, a tapering period over 60 months and with a type II mortality adjustment of 0.

[redacted] Based on this outcome, in addition to physiological advantages of sitting on respiratory function, clinicians considered it clinically plausible and reasonable to include a mortality adjustment factor for type II milestones or higher (three clinicians citing a range between 0.5-1, one clinician citing a range between 0.6-0.9). However, all clinicians also noted that there is an imperfect relationship between motor milestone attainment and respiratory function (often a lag before improvements in the latter). [redacted] In their opinion, if a patient is able to survive the first 2-3 years of life (and overcome respiratory infections), there is little reason to doubt they could potentially survive into adulthood.

The following assumptions were therefore applied in the model to reflect the updated data and clinical expert opinion:

- Do not use long-term data to guide extrapolation
- Taper the within HR trial to 1 over 120 months
- Mortality adjustment factor to be between 0.5 and 1.0 (0.75 in the base case)
- Apply general population mortality rates
- Patients discontinuing treatment assume same risk of death as patients in the RWC arm.

2.1.2 Transition Matrices

The transition matrices for RWC remain unchanged versus the previous assessment as patients in the sham control arm in ENDEAR transitioned to nusinersen in SHINE. The post-trial follow-up transition matrix is based on a mean monthly change in CHOP-INTEND from ENDEAR with alternative scenarios explored in sensitivity analyses. All clinical experts confirmed at the end of ENDEAR (month 13, age ~18.6 months), no motor milestone improvements would be expected without treatment and that a progressive decline in motor and respiratory function would reflect clinical practice.

The transition matrices for the nusinersen arm of the infantile onset model were updated with data from SHINE. The patient counts from baseline to day 394 were updated and new assessment points were included (day 578, 698, 818, and 938). The transition matrix based on the last assessment at day 938 was

not used due to the low number of patients that had reached this timepoint (N=5). The updated transition matrices for nusinersen are presented in Appendix A – nusinersen transition probabilities.

- New CHOP INTEND score rate of change scenarios for the nusinersen arm using SHINE data (dropdown row 150 Efficacy T1 sheet)
- New scenario that uses the last within trial-follow up transition matrix to extrapolate each arm.
- The percentage of patients worsening out of those patients that reach an improvement plateau was made health state specific (i.e. instead of assuming the same for all health states)
- Appendix B – List of changes since previous submission includes a step by step guide to replicate the results in the previous submission.

The updated transition matrices for the nusinersen arm were estimated based on observed data at each assessment point. However, the number of patients with an assessment significantly reduced after day 394.

Table 1. Number of patients alive at each assessment and health state distribution

Assessment day in trial	N	No milest.	Mild milest.	Mod. milest.	Sits wo	Stands w	Walks w	S/W w/o
Day 64	74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 183	67	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 302	60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 394	53	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 578	32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 698	17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 818	11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 938	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2. Model predictions of those alive

Assessment day in trial	No milest.	Mild milest.	Mod. milest.	Sits wo	Stands w	Walks w	S/W w/o
Day 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 183	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 302	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 394	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 578	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 698	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 818	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 30[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Based on model assumptions after trial follow-up.

[b] The model assumes that patients in no milestone health state after month 13 discontinue treatment, and therefore do not improve. However, some patients in SHINE were observed improving to the mild milestone and the moderate milestone health state after month 13.

[c] Most of the patients lost due to follow-up were last observed in the moderate milestone health state ([redacted]); and in all assessments (except at day 64) patients improved from the moderate milestone health state to the sits without support health state [redacted]moved to stands with assistance], [redacted]at days 183, 302, 394, 574, 698, and 818, respectively). The proportion of patients worsening from the moderate milestone health state was lower than the proportion improving in most assessments ([redacted]at days 183, 302, 394, 574, 698, and 818, respectively). Therefore, the percentages estimated in the sitting without support health state after day 578 based on the observed data (Table 1) are most likely underpredicting the true proportion of patients achieving sitting without support. The model prediction does not assume patients are lost due to follow-up; hence a larger proportion of patients achieve the sitting without support health state compared to the proportion based only on patients who had an observation. A scenario analysis assuming that patients lost due to follow-up remain in the same health state (i.e.

LOCF; which is a conservative assumption based on the observed data), resulted in a lower proportion of patients achieving the sitting without support and the standing unaided health states (Table 3).

Table 3. Scenario analysis: Model predictions of those alive assuming LOCF for patients lost due to follow-up

Assessment day in trial	No milest.	Mild milest.	Mod. milest.	Sits wo	Stands w	Walks w	S/W w/o
Day 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 183	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 302	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 394	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 578	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 698	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 818	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 30[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Based on model assumptions after trial follow-up.

2.1.3 Transition Matrices – Post- trial follow-up

After trial follow-up the model assumes that patients reach an improvement plateau at a defined month, and that a proportion of those patients reaching an improvement plateau progress/worsen as in the RWC arm. Before reaching the improvement, plateau patients will continue to improve based on the CHOP-INTEND rate of change. Treatment discontinuation is applied to all patients in the *No milestone* health state after 13 months, and to patients who worsen after reaching an improvement plateau.

Patients that keep improving

For the group of patients improving according to the transition matrix estimated from the rate of CHOP INTEND score increase, we have added an additional input which assumes that a proportion of patients receiving treatment are also allowed to worsen, but with the possibility to improve at a later time point as the patients remain on treatment. The rate of CHOP INTEND score change was also updated to reflect SHINE data. The base case uses the monthly rate of change observed from day 394 to day 818 ([redacted]), which is lower than the rate of change observed during the ENDEAR follow-up ([redacted]). It is worth noting that the updated rate of change is influenced by the number of patients with an assessment at day 818 and could be underestimated as many patients with higher rate of changes at earlier assessments have not reached day 818.

Patients improving could also achieve standing/walking unaided as patients in the CS3A trial were able to walk unaided and stand with assistance (one patient had achieved walking unaided at day 568 [1 out of 13 pts with at least a 568 visit; 8%]; of those patients with an assessment after day 568, 4 patients had achieved standing with assistance by their last assessment [days 631 to 820] [4 out of 13 pts with at least a 568 visit; 30.7% [not including the patient walking unaided]) .

The percentage of patients worsening who could still improve was based on a weighted average of patients improving after they had worsened in the previous assessment (Table 4).

The updated transition matrix for patients that keep improving after trial follow-up is presented in (Table 5).

Table 4. Percentage of patients improving at assessment day x, which had worsened in the previous assessment n (%)

	Day 183	Day 302	Day 394	Day 578	Day 698	Day 818	Weighted average
SHINE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5. Transition matrix applied to patients improving after trial follow-up

	No Milest.	Mild. Milest.	Mod Milest.	Sits w	Stands w	Walks w	S/W w/o
No Milest.							
Mild. Milest.							
Mod Milest.							
Sits w							
Stands w							
Walks w							
S/W w/o							

The model also includes an alternative scenario where the transition matrix used for patients improving is the same as the last observed transition matrix (day 818). However, the use of the last transition matrix (Appendix A – nusinersen transition probabilities, Table 28) will introduce caps to transitions that are not aligned with clinical expectations in the long term (i.e. after day 818, patients in the moderate milestone and sitting without support health states will never transition to other health states, except transitioning between each other; patients will never achieve higher milestones; patients will never lose all milestones).

Patients reaching an improvement plateau

Clinical expert opinion mentioned it will be unlikely that patients that have not reached the ability to stand by 5 or 6 years will achieve it at a later age. Similarly, they believed that patients not reaching the ability to walk before their 6th or 7th birthdays will never achieve that ability. Therefore, the base case assumes that patients in the *mild milestones*, *moderate milestones* and the *sits without support* health states reach an improvement plateau at 53 months in the model (i.e. 59 months of age; [mean age entering the model: 5.6 months]); and patients in the stands with assistance and higher health states reach an improvement plateau at 63 months in the model (i.e. 69 months of age) (Figure 6. Month at which patients reach an improvement plateau.

Figure 6. Month at which patients reach an improvement plateau

	User	Default
Month after which a proportion of patients still on treatment stop improving and remain in the same health state		
No milestones achieved	13	13
Mild milestones	53	53
Moderate milestones	53	53
Sits without support	53	63
Stands with assistance	63	63
Walks with assistance	63	63
Stands/Walks unaided	63	63
% patients still on treatment who stop improving (remain on the same health state or worsen)		
No milestones achieved	100%	100%
Mild milestones	100%	100%
Moderate milestones	100%	100%
Sits without support	100%	100%
Stands with assistance	100%	100%
Walks with assistance	100%	100%
Stands/Walks unaided	100%	100%

Patients worsening out of those that reach an improvement plateau

To determine the percentage of patients worsening from each health state we estimated a weighted average of the proportion of patients worsening at each assessment (based on transition matrices in Appendix A). We also estimated the percentage of patients worsening at the last assessment in the later

onset model (transition matrix at day 456; based on CHERISH data). Out of the four scenarios available (Table 6), the later onset proportions were selected for consistency with the later onset mode and clinical expert opinion expecting a higher proportion in the lower milestones would discontinue that in the higher milestones. It is worth noting that SHINE data did not show any patient worsening compared to their day 394 assessmentt [redacted]

Table 6. Proportion of patients worsening out of those that reach an improvement plateau

Health state	Last assessment CHERIH trial (day 450)	Weighted average last 3 SHINE assessments (days 578, 698, and 818)	Weighted average last 3 ENDEAR assessments (day 183, 302 and 394),	Weighted average last 6 assessment (days 183, 302, 394, 578, 698, and 818)
No milestones achieved	[redacted]	[redacted]	[redacted]	[redacted]
Mild milestones	[redacted]	[redacted]	[redacted]	[redacted]
Moderate milestones	[redacted]	[redacted]	[redacted]	[redacted]
Sits without support	[redacted]	[redacted]	[redacted]	[redacted]
Stands with assistance	[redacted]	[redacted]	[redacted]	[redacted]
Walks with assistance	[redacted]	[redacted]	[redacted]	[redacted]
Stands/Walks unaided	[redacted]	[redacted]	[redacted]	[redacted]

[a] Assumed the same as worsening from the Sits and rolls independently health state in the later onset model.
[b] Assumed the same as worsening from the Sits and crawls with hands and knees health state in the later onset model.
[c] Assumed the same as worsening from the Stands/Walks with assistance health state in the later onset model.
[d] Assumed the same as worsening from the Stands unaided health state in the later onset model.

2.1.4 Results of revisions to clinical parameters

Figure 7 presents the base-case overall survival which results in a mean of 8.58 and 2.14 LYs gained (undiscounted) for patients in the nusinersen and RWC arm, respectively. In natural history, survival varies significantly depending on the type of respiratory care received. Estimates at 24 months range from 1.3% to 25% [2, 3, 6] and could increase to 68% when patients are on non-invasive respiratory support [6]. The model predicts a 40.8% of patients in the RWC arm alive at 24 months which was viewed as reasonable by two clinicians, and marginally overestimated by the remaining clinicians, although all acknowledged the rapidly evolving standards of care (e.g. use of non-invasive or invasive ventilation) could impact these estimates in clinical practice.

Figure 7. Base case Overall survival

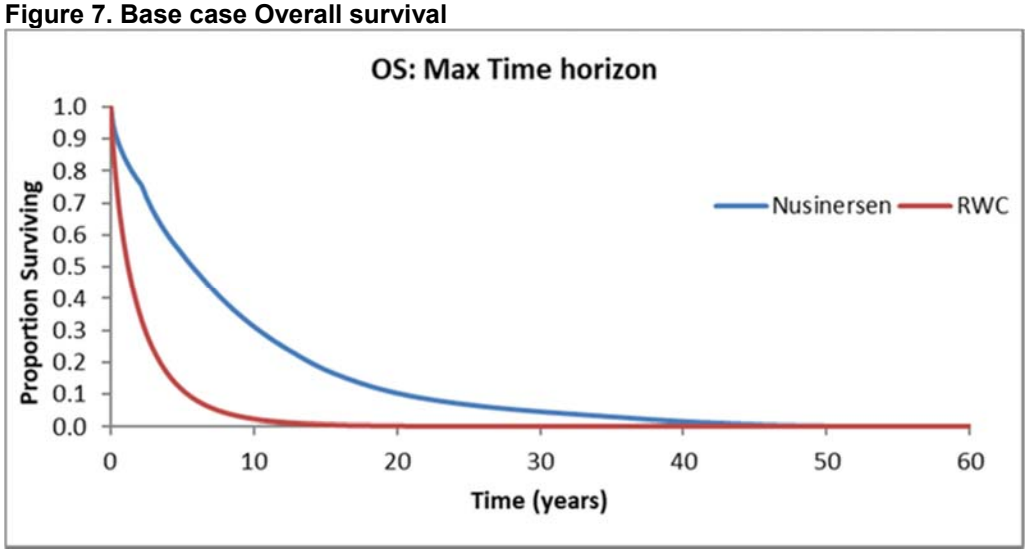


Figure 7 and Figure 8 present the Markov traces for the base-case analysis. The maximum proportions of patients in the nusinersen arm ever achieving type II milestones (sitting without support, standing with assistance, or walking with assistance) and type III milestones were 40.8% and 6.3%, respectively. The age caps at which patients stop improving have been incorporated according to clinical opinion.

Figure 8. Base case Markov Trace - nusinersen

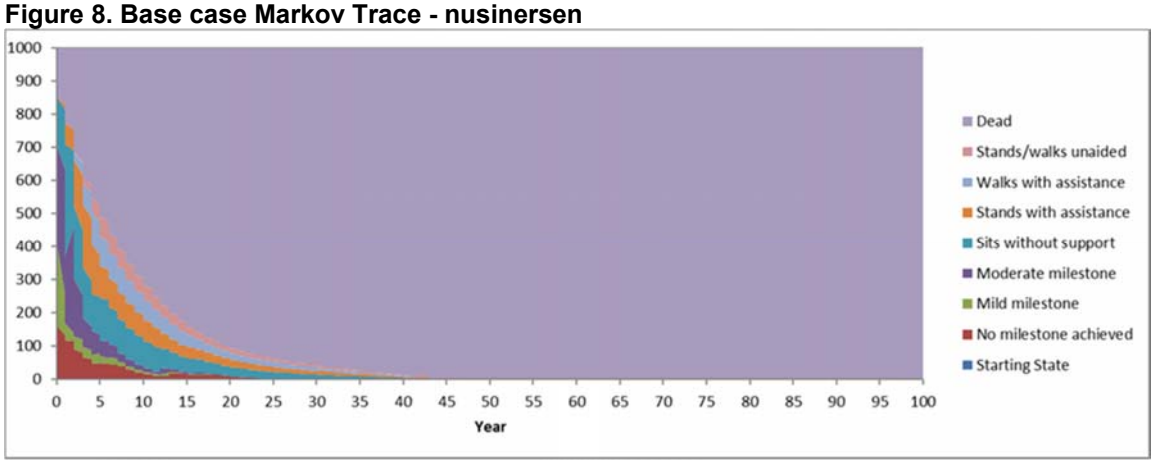
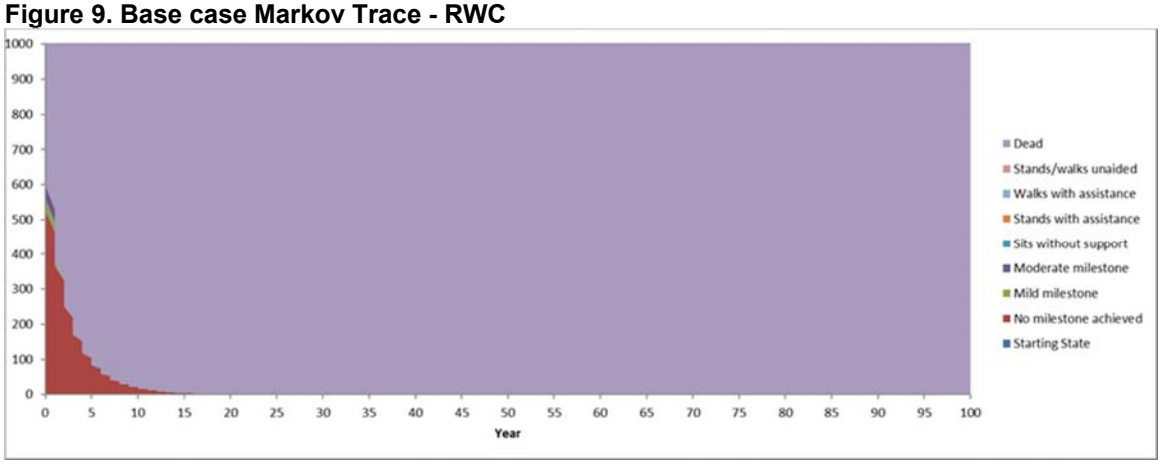


Figure 9. Base case Markov Trace - RWC



2.2 Later onset (type II/IIIa) SMA

The later onset model structure remains the same as in the previous submission. However similar to the updated approach to transition matrices in the infantile onset model, all 'sub-models' are now active (as opposed to 'plateauing' sub-models being redundant in the previous submission). It should be noted that a key change in this model versus the previous submission is the introduction of patients being able to lose the ability to sit from the *Sits without support but does not roll* health state based on the natural history literature and clinical expert opinion (see section 2.2.2). Furthermore, no additional extension study data has been incorporated into the model, the latest data cut is due to published in mid-2019. Clinical validation was therefore conducted on the economic model and assumptions used in the previous submission.

2.2.1 New scenarios and input updates

- New scenario that uses the last within trial-follow up transition matrix to extrapolate each arm
- The percentage of patients worsening out of those patients that reach an improvement plateau was made health state specific (i.e. instead of assuming the same for all health states) to address clinical expert opinion in the absence of longer-term data for later onset SMA
- New scenario which assumes that later onset patients can also lose the ability to sit as validated in the literature and clinical expert opinion

2.2.2 Transition Matrices

The transition matrices for the RWC arm remain unchanged in the base case, that is that post-trial follow-up a progressive decline is predicted. Considering the mean age at post-trial follow-up (mean baseline age: 43.4 months and the duration CHERISH at 15 months; ~58 months), clinicians considered that maximal motor milestones should have already been gained by this time point and therefore no significant improvement in motor milestones would be expected.

Patients that keep improving

For the group of patients improving according to the transition matrix estimated from the rate of HFMSE score increase, we have added an additional input which assumes that a proportion of patients receiving treatment are also allowed to worsen, but with the possibility to improve at a later time point as the patients remain on treatment. The percentage of patients worsening who could still improve was based on a weighted average of patients improving after they had worsened in the previous assessment (Table 7).

The updated transition matrix for patients that keep improving after trial follow-up is presented in (Table 8).

Table 7. Percentage of patients improving at assessment day x, which had worsened in the previous assessment n(%)

	Day 169	Day 253	Day 350	Day 450	Weighted average
CHERISH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 8. Transition matrix applied to patients improving after trial follow-up

	Sits no Roll.	Sits and Roll	Sits and Crawls	S/W w	S w/o	W w/o
Sits no Roll	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sits and Roll	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sits and Crawls	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S/W w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S w/o	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
W w/o	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The model also includes an alternative scenario where the transition matrix used for patients improving is the same as the last observed transition matrix (day 456). However, the use of the last transition matrix will introduce caps to transitions that are not aligned with clinical expectations in the long term (i.e. patients will never lose the ability to stand unaided or walk unaided; after day 456 no patient will reach these health states). Similarly, if the last observed transition matrix is used for the RWC arm it will introduce caps not aligned with natural history (patients will remain in the standing unaided and walking unaided health states; patients in the sit and crawls health state will remain there).

Patients reaching an improvement plateau

All of the clinical experts consulted stated it would be unlikely for patients that have not reached the ability to stand by 5 or 6 years to achieve it at a later age. Similarly, they believed that patients not reaching the ability to walk before their 6th or 7th birthday, will never achieve that ability. Therefore, the base case assumes that patients in the *Sits without support but does not roll*, *Sits and rolls independently, and Sits and crawls with hands and knees* health states reach an improvement plateau at 15 months in the model (i.e. 59 months of age; [mean age entering the model: 44 months]); and patients in the stands/walks with assistance and higher health states reach an improvement plateau at 25 months in the model (i.e. 69 months of age). Patients in the *Sits without support but does not roll* health state are assumed to all discontinue treatment after trial follow-up and follow the RWC transition matrix (Figure 10). This assumption and timepoint of benefit assessment were deemed reasonable by 3 of the 4 clinical experts consulted; one clinician thought a longer time period prior to the assessment of benefit at 24 months following treatment initiation would be more appropriate.

Figure 10. Month at which patients reach an improvement plateau

	User	Default
Month after which a proportion of patients still on treatment reach an improvement plateau and stay in current health state		
Sits without support but does not roll	15	15
Sits and rolls independently	15	15
Sits and crawls with hands and knees	15	15
Stands/Walks with assistance	25	25
Stands unaided	25	25
Walks unaided	25	25
% patients still on treatment who stop improving (remain on the same health state or worsen)		
Sits without support but does not roll	100%	100%
Sits and rolls independently	100%	100%
Sits and crawls with hands and knees	100%	100%
Stands/Walks with assistance	100%	100%
Stands unaided	100%	100%
Walks unaided	100%	100%

Patients worsening out of those that reach an improvement plateau

The percentage of patients worsening from each health state was estimated based on the proportion of patients worsening at each assessment in the CHERISH trial. Three scenarios were explored (Table 9), one which uses the percentage of patients worsening at the last assessment (transition matrix at day 456), one which estimates a weighted average from the last three assessments (day 274, 365 and 456) and one which used the maximum value of the last three assessments (day 274 365, and 456).

Table 9. Proportion of patients worsening out of those that reach an improvement plateau.

Health state	Last assessment CHERIH trial (day 450)[a]	Weighted average last 3 assessments (day 456, 365, and 274)	Max of last 3 assessments (day 456, 365, and 274)
Sits without support but does not roll	[redacted]	[redacted]	[redacted]
Sits and rolls independently	[redacted]	[redacted]	[redacted]
Sits and crawls with hands and knees	[redacted]	[redacted]	[redacted]
Stands/Walks with assistance	[redacted]	[redacted]	[redacted]
Stands unaided	[redacted]	[redacted]	[redacted]
Walks unaided	[redacted]	[redacted]	[redacted]

[a] Used in the base-case analysis, sits and rolls independently replaced with max of last assessment value based on clinical expert opinion where higher proportions would be expected to discontinue in the lower milestone health states.
[b] in the base case analysis, both health states were assumed to equal to the worsening % observed for stands/walks with assistance. Assuming 0% discontinuation from these health states would be deemed optimistic.

A key additional scenario was added to account for patients with type II SMA losing the ability to sit (applied to both arms). Although it should be noted that no patient lost the ability to sit within CHERISH in either arm (likely due to the homogenous population and short trial duration in addition to no WHO motor milestone definition for patients who are unable to sit), all clinical experts consulted considered this to be important especially when modelled over a life time horizon and is reflected in the natural history literature.

A study by Ge et al. 2012 of 105 Chinese patients with SMA type II found that the probability of maintaining independent sitting was 91.1% at 1 year and 2 years and 86.4% at 5 years [3] although it is unclear from

the publication whether these are ages or disease duration. A Dutch study, conducted by Wadman et al. 2018, reported a mean age at losing ability to sit of 8.6 years and 16.5 years for type IIa and IIb patients, respectively [7]. The model estimates a weighted average of the age at losing the ability to sit from the data reported by Wadman et al., 2018 (i.e. 12.2 years) and uses a linear interpolation from the end of trial follow-up to model the proportion of patients losing the ability to sit.

Given the time constraints and what is already considered an overly complex model, we elected not to introduce a new health state in the later onset model for the losing the ability to sit. The model therefore applies the proportion of patients losing the ability to sit to those patients in the *Sits without support but does not roll* health state and calculates the QALYs and health states costs using a weighted average based on the *Sits without support but does not roll* health state utility and the *moderate milestone* infantile onset health state utility, caregiver number and disutility, in addition to the type II and type I health state costs. The same assumptions were applied to both the RWC and nusinersen arm. In the RWC arm this results in the loss of the ability to sit without support in 50% of patients in the *sits without support but does not roll* healthstate by 12.2 years of age. This increases to 13.2 years of age when all type II health states are considered (*Sits without support but does not roll, Sits and rolls independently, Sits and crawls with hands and knees, Stands/Walks with assistance).* The impact of including loss of sitting without support is tested in sensitivity analyses.

2.2.3 Survival

Based on feedback from all the clinical experts consulted, the mean overall survival of 36.37 years (undiscounted) in the RWC arm was deemed appropriate. Therefore, no changes were made to the RWC survival predictions. Furthermore, all clinicians believed it was appropriate and clinically plausible from a physiological perspective to include a mortality adjustment for patients achieving type III milestones of standing/walking unaided with a range between 0.5 – 1.0.

The following assumptions were applied in the model:

- Patients achieving type III milestones have a survival closer to the general population (factor of 0.75). Clinical opinion considered the factor to be between 0.5 and 1.0.
- Apply general population mortality rates
- Patients discontinuing treatment assume same risk of death as patients in the RWC arm.

2.2.4 Results of clinical parameter revisions

Figure 11 presents the base-case overall survival which results in a mean of 38.48 and 36.67 LYs. gained (undiscounted) for patients in the nusinersen and RWC arm, respectively (20.11 and 19.68 LYS discounted).

Figure 11. Base case Overall survival

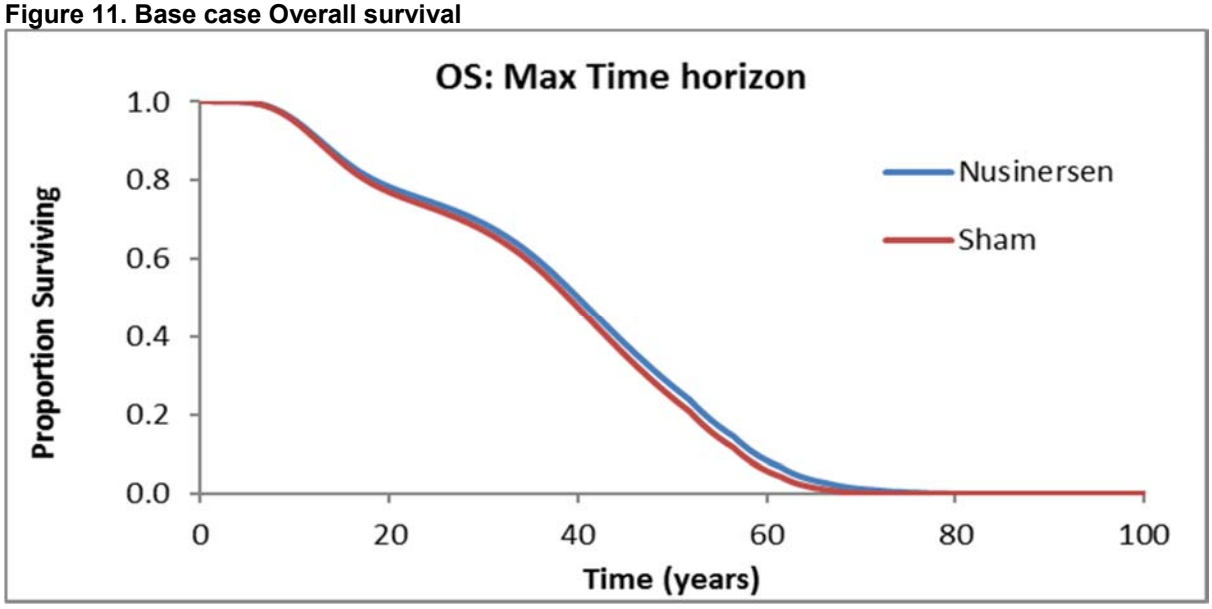


Figure 12 and

Figure 13 present the Markov traces for the base-case analysis. The maximum proportions of patients ever achieving type III milestones (standing unaided or walking unaided) was 14% and 7% in the nusinersen arm and RWC arm, respectively. The age caps at which patients stop improving have been incorporated according to clinical opinion. In natural history, the majority of type IIIa patients lose ambulation by the time they reach puberty. Table 10 presents a summary of the time at which type IIIa patients lose ambulation according to natural history studies.

Table 10. Natural history data type IIIa patients

	Zerres et al., 1997 [8]	Chung et al., 2004 [9]	Ge et al., 2012 [3]	Wadman et al., 2018 [7]
10 years	70.3%[a]	75%	76.7%	NA
15 years	NA	NA	NA	50%[b]
20 years	NA	50%	NA	NA
40 years	22.0%[a]	38%	NA	NA

NA = not available

In a long-term study conducted by Werlauff et al. 2012 on muscle strength in seven patients with SMA type III with a median follow-up of 17 years, three patients with SMA type III had lost the ability to stand and walk at ages 4, 8, and 9 years [10].

[a] Probability at 10 and 40 years after disease onset.

[b] Mean age at which patients lost ability to stand or walk with aids.

At end of trial follow-up (a mean age of 59 months) the proportion of patients in type III health states (standing unaided or walking unaided) predicted by the model in the RWC arm was 6.5%. Using the mean monthly decline in HFMSE results in a pessimistic proportion of patients remaining in these health states (out of the 6.5%) at 10, 15, 20, and 40 years of age of 26.5%, 7.2%, 1.9% and 0%, respectively. Therefore, in the base case, the probability of progression in the RWC arm from the standing unaided and walking unaided health states was reduced to 2% (Efficacy T2 sheet I180 and I185) resulting in estimates at 10, 15, 20 and 40 years old of 77.9%%, 60.3%, 46.0%, and 15.3%, respectively.

Figure 12. Base case Markov Trace - Nusinersen

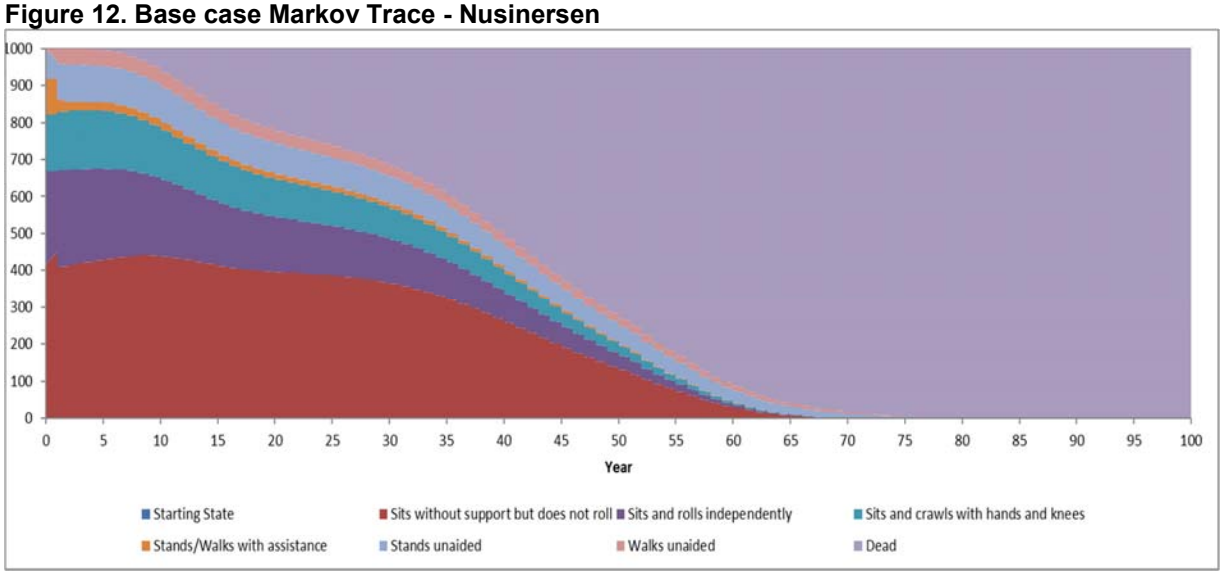
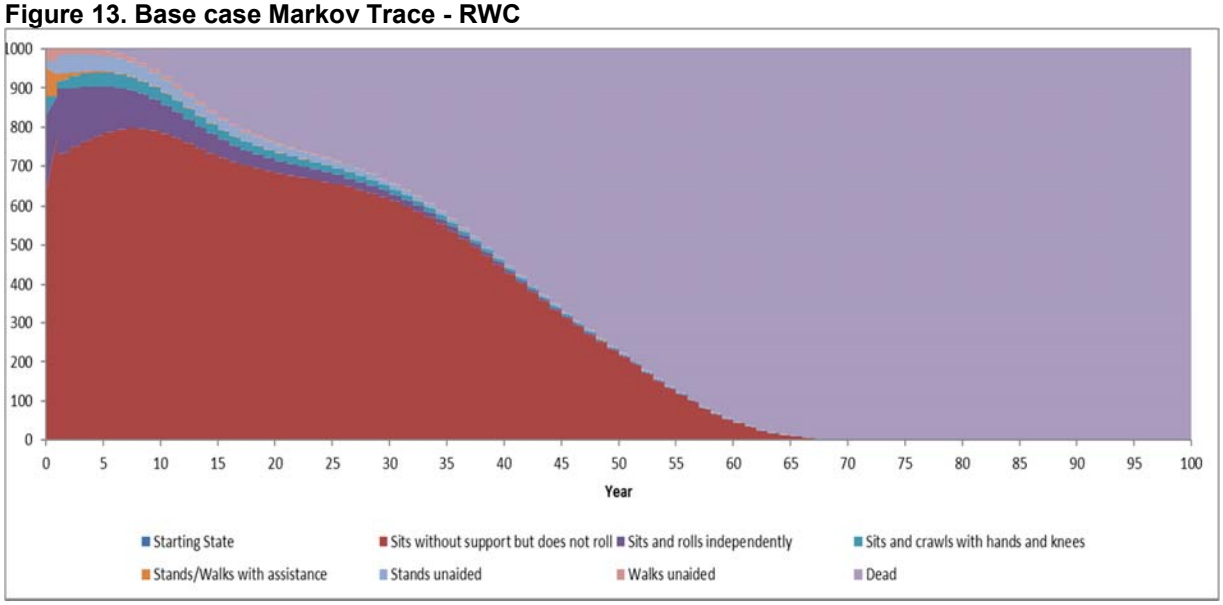


Figure 13. Base case Markov Trace - RWC



2.3 Health states costs

Table 11 presents the health state cost sources used in the previous submission based. Bastida et al. (2016) [11] provided insight into the disease burden in SMA, including UK data on costs. However, this research was purely based on caregiver responses for a small number of patients (7 for type I, 20 for type II and 7 for type III) and lacked differentiation of practice across the UK. Following discussions at the committee meeting on 23rd October and comments received during the public consultation, the Bastida et al (2016) [11] estimates were deemed to lack face validity and significantly underestimate the likely disease management costs. All clinical experts consulted supported this conclusion. This cost source has therefore not been considered in further analyses.

UK specific literature on the economic burden associated with SMA is sparse. Therefore in 2017, Biogen conducted a survey including a sample of leading paediatric neurological consultants representing nine UK centres to evaluate best estimates related to these points. The responding centres were caring for a total of 272 SMA patients at the time of the survey (September 2017). Further details on the survey and results can be found in Appendix C - RWE survey.

On the basis of responses from across the centres, using weighted averages, the total cost for a typical patient per year was estimated to be £77,968 for type I, £58,185 for type II and £20,230 for type III (Table 11).

Table 11. Health state costs considered in the previous submission

SMA type	RWE survey 2017 [12]	Bastida et al. (2016) [11]
SMA type I	£77,968	£18,110
SMA type II	£55,185	£9,634
SMA type III	£20,229	£2,806

A breakdown of cost components and drivers are presented in Table 12. For type I patients, the largest proportion of costs (67%) arises from inpatient admissions (£52,045). Patients being admitted into intensive care are the largest driver of the £52,045, costing £32,216 per patient per year. Major clinical interventions are also a significant component of total costs for type I patients, with this cost largely driven by the requirement for permanent non-invasive ventilation >16 hours a day in this population (£5,019). The other major cost driver of major clinical interventions for type I patients was gastrostomy (£4,509).

In contrast to type I, the major cost drivers in later onset patient groups (type II and III) are major clinical interventions. Type II patients experience the highest annual cost for this out of all SMA types. While the key driver of major clinical interventions in type I patients was permanent non-invasive ventilation >16 hours per day, for type II and III patients this changes to scoliosis surgery (costing £20,032 and £15,360 per patient per year, respectively). The figures for this (in both subtypes) were driven by Leeds, Newcastle and Great Ormond Street Hospital (GOSH).

Table 12. RWE survey cost breakdown, weighted averages across centres

Cost element	Type I	Type II	Type III
Inpatient admissions	£52,045	£11,186	£2
Major clinical interventions	£12,175	£36,156	£15,483
Health materials	£5,613	£4,599	£1,059
Scheduled hospital visits	£3,030	£2,552	£1,487
Non-scheduled hospital visits	£2,566	£611	£177
Medical test utilisation	£1,813	£2,383	£1,433
Testing methodologies	£645	£622	£534
Drug usage	£81	£76	£54
Total	**£77,968**	**£58,185**	**£20,230**

Table 13 further disaggregates costs specific to the centres analysed. It should be noted that most of the variation between centres is driven by a lack of response by some centres to certain questions (which is accounted for in the total cost calculation by using weighted averages by patient numbers at each centre, with non-responding centres excluded from the weighted average for particular questions).

Table 13. Total annual costs per SMA type by centre

Treatment centre	Total Annual Cost		
	Type I	Type II	Type III
Leeds	[redacted]	[redacted]	[redacted]
Newcastle	[redacted]	[redacted]	[redacted]
Glasgow	[redacted]	[redacted]	[redacted]
GOSH	[redacted]	[redacted]	[redacted]
Belfast	[redacted]	[redacted]	[redacted]
Oswestry	[redacted]	[redacted]	[redacted]
Cardiff	[redacted]	[redacted]	[redacted]
Dundee	[redacted]	[redacted]	[redacted]
Evelina	[redacted]	[redacted]	[redacted]

All clinicians consulted noted that the trend in costs from the survey were appropriate (highest cost in type I, followed by type II and type III accruing the lowest cost). However, all clinicians expected the costs for type I to be higher than estimated driven by more costs accrued in major clinical interventions (closer to a factor of 2 which was also supported by PAGs at the committee discussions in October). A potential rationale for this could be the timing at which the survey was conducted (September 2017), when the approach to type I care was palliative (the EAP NHSE commissioning policy was only published in August 2017 allowing access to free of charge stock for type I patients). Moreover, the approaches to standards of care have changed significantly (new guidance published in 2018) with approaches to the four core pillars of care (respiratory, nutritional, gastrointestinal and orthopaedic) being more interventional (e.g. use of non-invasive or invasive ventilation if appropriate) despite lack of treatment access [13].

With regards to variations across the treatment centres surveyed, clinicians noted that this is likely caused by several factors including:

- Case load variances
- Some centres (e.g. Oswestry) only accounted outpatient care with inpatient admissions likely referred to other centres
- Patients with more severe disease being referred to research centres (e.g. GOSH & Newcastle)
- Variations in service provision and adoption of the latest consensus guidelines to standards of care
    - More likely to be adopted early in centres such as GOSH and Newcastle.

Clinicians therefore suggested that only GOSH and Newcastle were used in the weighted average for the health state costs (covering [redacted] [60%] of patients in the survey). Table 14 presents the results of basing

the weighted average of these two centres and applying a cost adjustment factor of 2 to the type I estimates. This cost factor is tested is sensitivity analyses.

Table 14. Weighted average of health states costs across GOSH & Newcastle

	Type I	Type II	Type III
Weighted Average GOSH & Newcastle only	£74,107	£68,322	£21,765
Weighted Average with adjustment to type I[a]	£148,214	£68,322	£21,765

[a] used in the base case

2.4 Patient and caregiver utilities

2.4.1 Patient utilities

Table 15 presents the patient utilities sources considered in the previous submission (except the Biogen clinical adviser estimates). The clinical experts consulted were asked to comment on the appropriateness of these sources. An additional analysis using the mid-points between ERG clinical adviser estimates and case vignette were presented to clinicians.

In prior committee discussions, the PedsQL values were deemed to lack face validity due to the high estimates for the lowest motor milestones and the minimal differentiation compared to the best health state. This conclusion was confirmed by all consulted clinical experts. Furthermore, whilst the case vignettes produced a more plausible trend, clinical experts also questioned the face validity of the negative utility assigned to *Sits without support* or lower milestones in infantile onset (although 2 clinicians believed *No milestones* and potentially *Mild milestones* should be attributed negative/near death values closer to the mid-point between the ERG estimates and the case vignette study) in addition to the near death values assigned to the *Sits without support but does not roll* and *Sits and rolls independently* health states. Both of these sources as presented were therefore not considered in further analyses.

Table 15. Patient utility sources

Health state	PedsQL	Case vignette	ERG clinical advisers	Biogen clinical advisers [a]
Infantile Onset (type I SMA)				
No Milestone Achieved	[redacted]	-0.240	0.200	-0.020
Mild Milestones	[redacted]	-0.120	0.250	0.100
Moderate Milestones	[redacted]	-0.170	0.350	0.200
Sits Without Support	[redacted]	-0.040	0.600	0.400
Stands With Assistance	[redacted]	0.040	0.650	0.650
Walks With Assistance	[redacted]	0.520	0.750	0.750
Stands/Walks Unaided	[redacted]	0.710	0.850	0.850
Later Onset (type II & IIIa SMA)				
Sits Without Support But Does Not Roll	[redacted]	0.040	0.600	0.400
Sits and Rolls Independently	[redacted]	0.040	0.600	0.450
Sits and Crawls With Hands and Knees	[redacted]	0.100	0.600	0.500
Stands/Walks With Assistance	[redacted]	0.390	0.750	0.700
Stands Unaided	[redacted]	0.720	0.850	0.850
Walks Unaided	[redacted]	0.720	0.850	0.850

[a] used in the base case analysis

All clinical experts consulted believed the ERG estimates were clinically plausible for the higher milestones (stands with assistance or higher) in both infantile and later onset SMA. However, 3 clinicians believed *Sitting without support* valued at 0.6 were too high (and the mid-point of 0.32 being too low), citing more plausible estimates should lie between 0.4-0.5. Moreover, clinicians believed that differentiation should exist between *Sits without support but does not roll*, *Sits and rolls independently, Sits and crawls with high and knees* between these values reflecting the differentiation in independency, self-care, transfers etc. For the *No*, *Mild* and *Moderate milestones* in infantile onset, 3 clinicians believed the mid-point value between the ERG estimates and the case vignette study would be more appropriate which reflected a negative value for *No milestones* achieved and positive values for *Mild* and *Moderate milestones*.

Based on this feedback, Biogen have included an additional utility source as presented in Table 15 and are used in the base case with the ERG values used in sensitivity analyses. It should be noted that both the ERG and Biogen estimates are non-preference based estimates of HRQoL despite better validity.

In the base case, based on clinical adviser estimates derived by Biogen, patients in the nusinersen arm and the RWC arm accrued 2.64 and 0.00 (due to QALYs accrued in the higher health states being offset by the no milestone health state) patient QALYs (discounted), respectively. Use of the ERG clinical adviser estimates resulted in 3.41 and 0.42 patients QALYs respectively for nusinersen and RWC. The ERG values produced higher QALYs for the due to the higher values across the worst four health states.

2.4.2 Caregiver utilities

Carer impacts are not explicitly part of the NICE reference case but can be taken into account where they are considered to be important. However, the methodology for assessing caregivers' quality of life is not well developed. Like other orphan diseases, there is little quantitative evidence about the impact of SMA on caregivers' HRQoL or other important facets of their lives. However, for SMA there is now substantial qualitative evidence on the impact on caregivers.

This is particularly strengthened by the two surveys, one conducted by the SMA UK (previously known as SMA Support) and the other supported by Biogen, that explore the impact of SMA on patients and their caregivers. According to the survey findings, several caregivers are affected, and this extends beyond immediate family members. Also, due to complexity of the disease, informal caregivers provide extensive support to SMA patients, which has detrimental effect on their quality of life. Very often, the carers are forced to reduce their working hours, leave employment and change career goals. On top of that, as SMA patients have complex and extensive needs, carers are often faced with additional OOP expenses, not typically covered by the statutory health insurance, as even heard during the second AC meeting. Additional information can be found in Appendix D- Patient advisory group surveys. The surveys support and validate the extensive resource use and cost burden (some of these potentially uncaptured in the RWE survey [12]) of SMA across its subtypes and provides further insights into the caregivers' burden.

Caregiver QALYs are linked to patients' life years, not caregiver life years; analogous to patient QALYs, carer QALYs are calculated as patient life years multiplied by caregiver utilities. This can give rise to potentially counterintuitive results:

- Caregiver utilities can be adversely affected by improved patient survival, resulting in an adverse (and counterintuitive) impact on carer QALYs of improving patient survival.
- Increasing the number of caregivers affected can, paradoxically, result in a deterioration of the ICER.
- An HRQoL adjustment can be made for bereavement but there is little evidence to quantify the magnitude or duration of this effect.

- Caregiver HRQoL impact can be modelled by a positive utility or a utility decrement (a negative amount) but there is no clear guidance on which is more appropriate or how it should be implemented.

There are several options for modelling health benefits of caregivers. In the previous submission, carer utilities included in the model submitted to NICE were considered by the ERG to lack face validity. Carer utilities by SMA type from the Bastida et al. (2016) [11] study were used by the ERG but the appraisal committee considered that the ERG's approach lacked face validity whereby the best health state was associated with the worst utility/greatest disutility.

Utilising the caregiver utilities obtained by Bastida et al. (2016) [11], including those from other countries, 'Narrow range' and 'Wide range' options have been tested. The lower and upper bounds of the caregiver utility values for both the infantile and the later onset model have been calculated using the similar approach, with an additional assumption that utility value of the *Sits without support* from the infantile onset model is equivalent to utility value of the *Sits without support but does not roll* from the later onset model.

The 'Wide range' used in the base case implements the average utility in the Spanish arm of the study (0.484) for the lower bound and the EQ-5D score for the general population of the UK (0.915). The Spanish results are published in a peer-reviewed journal [14] and also had the highest number of respondents out of the 4 countries. The 'Narrow range' is used in scenario analyses and, for the infantile onset model, implements the upper and lower utilities by SMA type for the UK arm of the study (0.63 and 0.88). Caregiver utilities are shown in Table 16. Caregiver utilities implemented in the model and are implemented in the economic models as disutilities to the UK general population using the 'Wide range' values and 3 caregivers in the base case for infantile onset and 2 caregivers in the later onset model; the "Narrow range" is tested in scenarios.

Between the upper and lower bounds, equal incremental changes in utility are applied as health states progress from worst to best (top to bottom in Table 16. Caregiver utilities implemented in the model). The two best health states in later onset SMA are assigned the same utility, as in the case vignette study and ERG clinical advisor estimates.

Table 16. Caregiver utilities implemented in the model

Health state	Carer utilities: Narrow range	Carer utilities: Wide range [a]
Infantile Onset (type I SMA)		
No Milestone Achieved	0.630	0.484
Mild Milestones	0.672	0.556
Moderate Milestones	0.713	0.628
Sits Without Support	0.755	0.700
Stands With Assistance	0.797	0.771
Walks With Assistance	0.838	0.843
Stands/Walks Unaided	0.880	0.915
Later Onset (type II & IIIa SMA)		
Sits Without Support But Does Not Roll	0.755	0.700
Sits and Rolls Independently	0.776	0.743
Sits and Crawls With Hands and Knees	0.797	0.786
Stands/Walks With Assistance	0.818	0.807
Stands Unaided [b]	0.880	0.915
Walks Unaided [b]	0.880	0.915

[a] used in base case setting

[b] uses the same value for consistency with the infantile onset model

In the infantile onset model, over a 60-year time horizon, caregiver QALYs were estimated using the caregiver "Wide range" disutilities scenario which resulted in -4.48 and -2.61 (discounted) caregiver QALYs for

the nusinersen arm and RWC arm, respectively (or -1.49 and -0.87, respectively per caregiver). Using the caregiver “Narrow range” disutilities scenario which resulted in -3.34 and -1.77 (discounted) caregiver QALYs for the nusinersen arm and RWC arm, respectively (or -1.1 and -0.6, respectively per caregiver). The caregivers in the nusinersen arm were associated with more QALYs lost due to the longer survival of patients.

In the later onset model, over an 80-year time horizon, caregiver QALYs were estimated using the caregiver “Wide range” disutilities scenario which resulted in -9.02 and -12.40 (discounted) caregiver QALYs for the nusinersen arm and RWC arm, respectively assumed 2 caregivers for later onset patients that do not lose the ability to sit and 3 caregivers for those that do lose this ability. Using the caregiver “Narrow range” disutilities scenario which resulted in -6.94 and -9.00 (discounted) care-giver QALYs for the nusinersen arm and RWC arm, respectively. In the later onset model, as there is only a marginal gain in survival, benefits to caregivers are observed in the nusinersen arm as a higher proportion of patients reach better health states and smaller proportion lose the ability to sit by puberty.

2.5 Proposed commercial offer

Following the appraisal committee meeting on 23rd October 2018, Biogen has revised and simplified the commercial offer for nusinersen dependent on commissioning being agreed across both infantile and later onset SMA to reduce the ICERs. Biogen also remain committed to managed access agreement/data collection as outlined in the previous submission to better understand long-term outcomes and mitigate risk to the NHS to ensure access is both managed and sustainable.

The previous offer included:

The revised offer includes:

3. Updated Cost-Effectiveness Results

3.1.1 Methods in infantile onset model (type I SMA)

An overview of the base case settings is provided in Appendix E – Base case settings . This section outlines the preferred base case analysis applied to infantile onset model. The preferred analysis includes: (i) the use of a common initial distribution across health states for both treatment groups; (ii) mean monthly CHOP-INTEND increase with nusinersen from day 394 to day 818 in SHINE, (iii) age caps on motor milestone attainment (Figure 6) at which 100% of patients experience an improvement plateau, (iv) 5.7% nusinersen patients worsen each cycle but can improve in subsequent cycles up to the age caps for improvement plateau; (v) the proportion of patients reaching an improvement plateau which discontinue therapy and worsen as in RWC based on consistency with the later onset model (iii) adjustment to health state costs estimated by RWE survey, 2017 based on expert opinion; (iv) the inclusion of scoliosis assumptions aligned with later onset and clinical expert opinion; (v) the use of patient utilities from clinical advisors to Biogen; (vi) use of the adjusted "wide range" caregiver utilities and (vii) the inclusion of 2.5 caregivers supported by PAG surveys. Additionally, the infantile onset model also included: (i) mortality adjustment factor (base case 0.75) and (ii) HR tapered over 120-month period. All analyses were undertaken by assuming £75,000 nusinersen vial price and the commercial offer using the deterministic version of the revised cost-effectiveness model.

Additional sensitivity analyses were performed to explore: (i) a slow rate of CHOP-INTEND decline in RWC (ii) a range of type II mortality adjustments based on clinical expert opinion; (iii) increases to age caps for improvement plateau in motor milestones; (iv) alternative assumptions to the proportion of patients who can worsen and improve in subsequent cycles; (v) alternative assumptions to the proportion of patients who discontinue therapy and following RWC transition matrix (vi) altering cost factors for RWE study 2017; (vii) patient utility sources and caregiver utility ranges, (viii) patient subgroups based on disease duration;

The methods used to implement these analyses in the early onset model are described below.

Exploratory analysis 1: Slower rate of decline in CHOP-INTEND for the usual care arm

In this scenario, a mean monthly rate of CHOP-INTEND decline of 0.11 was used instead of [redacted] in the base case.

Exploratory analysis 2-3: Use of alternative mortality adjustment factors

In these scenarios, the type II mortality adjustment factor in varied at 0.5 and 1.

Exploratory analysis 4: Increases in age caps for improvement plateau

All health state improvement plateau ages are increased by 12 months excepted for the *no milestones* state

Exploratory analysis 5-6: Alternative assumptions regarding proportion of patients who worsen and can subsequently improve

Two additional scenarios were undertaken: (i) 11.4% of patients stop improving and follow RWC transition matrix, double that of the base case (ii) 2.85% of patients stop improving and follow RWC transition matrix, two times lower than in base case (except for discontinuation due to scoliosis surgery)

Exploratory analysis 7-8: Alternative assumptions to the proportion of patients who discontinue therapy and following RWC transition matrix

Two scenarios were explored: (i) Weighted average last 6 assessment (days 183, 302, 394, 578, 698, and 818) as presented in Table 6; (ii) values in the base case doubled

Exploratory analysis 9: Alternative assumptions regarding health state costs

An analysis using a cost adjustment factor of 1.5 for type I SMA was explored

Exploratory analysis 10: Alternative assumptions regarding patient utilities

An analysis was undertaken using utilities reported by the ERG clinical advisors

Exploratory analysis 11-12: Alternative assumptions regarding caregiver utilities

Two alternative analyses were assessed: i) using 'narrow range' estimates; ii) reducing the number of caregivers to 1

3.1.2 Results of the exploratory analyses – infantile onset SMA

The results of the company's base case and exploratory analyses are shown in Table 17 for £75,000 vial price and Table 18 for the revised commercial offer.

The base case scenario at £75,000 vial price has an ICER of £718,184 per QALY gained for patients and £2,482,192 per QALY gained including patient health gains and caregiver QALY losses. Respective numbers implementing the commercial offer are [redacted] per QALY gained for patients and [redacted] per QALY including caregiver perspective.

Application of the more optimistic assumption regarding infantile onset mortality, reduces the ICER as despite further disease management costs in additionally survived year, more QALY gains for the patient are accrued. If the proportion of patients who worsen but then can subsequently improve is increased, the ICER increases, predominantly due to QALY losses for the patient and the prolonger burden on the caregiver. If the last observed matrix for patients worsening is used, the ICER decreases slightly, predominantly due to QALYs gains; this particular scenario may be considered optimistic from the perspective that patients in the best two health states plateau and do not worsen (due to no worsening observations in ENDEAR/SHINE from these health states). Use of the ERG clinical advisor values marginally increases the ICER, predominantly due to high utility values for type I and type II health states. Changes to the health state costs have a small impact on the ICER as too did the age at which an improvement plateau is implemented. Reducing the caregiver numbers bring the patient and patient + caregiver ICERs together since the additional survive impacts only 1 caregiver.

In all of the analyses conducted, nusinersen would not be considered cost-effective at zero price. This conclusion is predominantly due to the high costs of disease management associated across type I and type II health state accrued in the years of additional survival. Resulting ICERs are approximately £100K per QALY gained for the patient only. Even with the most optimistic settings used (e.g. removing the age caps for improvement plateau, all patients continue to improve only, a mortality adjustment factor of 1, no cost-factor for type I patients, Biogen clinical adviser utility estimates or ERG clinical adviser estimates) the resulting ICER remains above the standard willingness to pay threshold in an STA for the patient only and even higher for the patient and caregiver. Only when disease management costs are significantly reduced across all types (e.g. use of Bastida et al, 2016) does this fall under standard willingness to pay thresholds, however these estimates have been discredited by clinical experts and patient advisory groups.

Table 17. Infantile onset model exploratory analyses, list price

Option	QALYs (patient)	QALYs (caregivers)	Cost	Inc. QALYs (patient)	Inc. QALYs (caregivers)	Inc. cost	ICER (patient)	ICER (patient+ caregiver)
Revised base case								
Nusinersen	2.64	-4.48	£2,200,847	2.64	-1.88	£1,897,211	£718,184	£2,482,192
RWC	0.00	-2.61	£303,635	-	-	-	-	-
S1 – Slower RWC arm decline in CHOP-INTEND								
Nusinersen	2.86	-4.45	£2,205,521	2.84	-1.88	£1,901,885	£669,977	£1,978,163
RWC	0.02	-2.58	£303,635	-	-	-	-	-
S2 – Later onset mortality adjustment applied (0.5)								
Nusinersen	1.99	-4.02	£1,891,137	1.99	-1.42	£1,587,502	£798,441	£2,779,726
RWC	0.00	-2.61	£303,635	-	-	-	-	-
S3 – Later onset mortality adjustment applied (1)								
Nusinersen	4.37	-5.61	£3,010,067	4.37	-3.00	£2,706,431	£619,276	£1,974,968
RWC	0.00	-2.61	£303,635	-	-	-	-	-
S4 – Increases in ages for improvement plateau								
Nusinersen	2.85	-4.35	£2,224,663	2.85	-1.74	£1,921,028	£674,434	£1,730,278
RWC	0.00	-2.61	£303,635	-	-	-	-	-
S5 – Proportion of patients who can worsen and subsequently improve doubled								
Nusinersen	2.22	-4.61	£2,110,857	2.22	-2.00	£1,807,222	£815,343	£8,525,240
RWC	0.00	-2.61	£303,635	-	-	-	-	-
S6 – Proportion of patients who can worsen and subsequently improve halved								
Nusinersen	2.88	-4.39	£2,241,575	2.88	-1.78	£1,937,940	£673,475	£1,770,266
RWC	0.00	-2.61	£303,635	-	-	-	-	-
S7 – Proportion of patients who discontinue per cycle based on last observed assessment without adjustments								
Nusinersen	2.72	-4.44	£2,228,077	2.71	-1.83	£1,924,442	£709,106	£2,176,309
RWC	0.00	-2.61	£303,635	-	-	-	-	-
S8 – Proportion of patients who discontinue per cycle doubled								
Nusinersen	2.41	-4.48	£2,085,304	2.40	-1.87	£1,781,668	£740,938	£3,325,249
RWC	0.00	-2.61	£303,635	-	-	-	-	-
S9 – Health state costs adjustment factor for type 1 (1.5)								
Nusinersen	2.64	-4.48	£2,108,426	2.64	-1.88	£1,877,754	£710,818	£2,456,735
RWC	0.00	-2.61	£230,672	-	-	-	-	-
S10 – ERG clinical advisors' patient utilities								
Nusinersen	3.41	-4.48	£2,200,847	2.99	-1.88	£1,897,211	£634,232	£1,703,059

Option	QALYs (patient)	QALYs (caregivers)	Cost	Inc. QALYs (patient)	Inc. QALYs (caregivers)	Inc. cost	ICER (patient)	ICER (patient+ caregiver)
Usual care	0.42	-2.61	£303,635	-	-	-	-	-
S11 – 'Narrow range' caregiver utilities								
Nusinersen	2.64	-3.34	£2,200,847	2.64	-1.56	£1,897,211	£718,184	£1,761,063
RWC	0.00	-1.77	£303,635	-	-	-	-	-
S12 – Number of caregivers 1								
Nusinersen	2.64	-1.49	£2,200,847	2.64	-0.63	£1,897,211	£718,184	£941,126
RWC	0.00	-0.87	£303,635	-	-	-	-	-

Table 18. Infantile onset model exploratory analyses with commercial offer

Option	QALYs (patient)	QALYs (caregivers)	Cost	Inc. QALYs (patient)	Inc. QALYs (caregivers)	Inc. cost	ICER (patient)	ICER (patient+ caregivers)
Revised base case								
Nusinersen	2.64	-4.48	[redacted]	2.64	-1.88	[redacted]	[redacted]	[redacted]
RWC	0.00	-2.61	[redacted]	-	-	-	-	-
S1 – Slower usual care arm decline in CHOP-INTEND								
Nusinersen	2.86	-4.45	[redacted]	2.84	-1.88	[redacted]	[redacted]	[redacted]
RWC	0.02	-2.58	[redacted]	-	-	-	-	-
S2 – Later onset mortality adjustment applied (0.5)								
Nusinersen	4.37	-5.61	[redacted]	4.37	-3.00	[redacted]	[redacted]	[redacted]
RWC	0.00	-2.61	[redacted]	-	-	-	-	-
S3 – Later onset mortality adjustment applied (1)								
Nusinersen	1.99	-4.02	[redacted]	1.99	-1.42	[redacted]	[redacted]	[redacted]
RWC	0.00	-2.61	[redacted]	-	-	-	-	-
S4 – Increases in ages for improvement plateau								
Nusinersen	2.85	-4.35	[redacted]	2.85	-1.74	[redacted]	[redacted]	[redacted]
RWC	0.00	-2.61	[redacted]	-	-	-	-	-
S5 – Proportion of patients who can worsen and subsequently improve doubled								
Nusinersen	2.22	-4.61	[redacted]	2.22	-2.00	[redacted]	[redacted]	[redacted]
RWC	0.00	-2.61	[redacted]	-	-	-	-	-
S6 – Proportion of patients who can worsen and subsequently improve halved								
Nusinersen	2.88	-4.39	[redacted]	2.88	-1.78	[redacted]	[redacted]	[redacted]
RWC	0.00	-2.61	[redacted]	-	-	-	-	-
S7 – Proportion of patients who discontinue per cycle based on last observed assessment								
Nusinersen	2.41	-4.48	[redacted]	2.40	-1.87	[redacted]	[redacted]	[redacted]
RWC	0.00	-2.61	[redacted]	-	-	-	-	-
S8 – Proportion of patients who discontinue per cycle doubled								
Nusinersen	2.41	-4.48	[redacted]	2.40	-1.87	[redacted]	[redacted]	[redacted]
RWC	0.00	-2.61	[redacted]	-	-	-	-	-
S9 – Health state costs adjustment factor for type I (1.5)								
Nusinersen	2.64	-4.48	[redacted]	2.64	-1.88	[redacted]	[redacted]	[redacted]
RWC	0.00	-2.61	[redacted]	-	-	-	-	-
S10 – ERG clinical advisors' patient utilities								
Nusinersen	3.41	-4.48	[redacted]	2.99	-1.88	[redacted]	[redacted]	[redacted]

Option	QALYs (patient)	QALYs (caregivers)	Cost	Inc. QALYs (patient)	Inc. QALYs (caregivers)	Inc. cost	ICER (patient)	ICER (patient+ caregivers)
RWC	0.42	-2.61	[redacted]	-	-	-	-	-
S11 – 'Narrow range' caregiver utilities								
Nusinersen	2.64	-3.34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RWC	0.00	-1.77	[redacted]	-	-	-	-	-
S12 – Number of caregivers 1								
Nusinersen	2.64	-1.49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RWC	0.00	-0.87	[redacted]	-	-	-	-	-

3.1.3 Methods in later onset model (SMA type II/IIIa)

An overview of the base case settings is provided in Appendix E – Base case settings . This section outlines the preferred base case analysis applied to later onset model. The preferred analysis includes: (i) the use of a common initial distribution across health states for both treatment groups; (ii) mean monthly HFMSE increase with nusinersen to day 450 in CHERISH, (iii) age caps on motor milestone attainment (Figure 10) at which 100% of patients experience an improvement plateau, (iv) 4.5% nusinersen patients worsen each cycle but can improve in subsequent cycles up to the age caps for improvement plateau; (v) the proportion of patients reaching an improvement plateau which discontinue therapy and worsen as in RWC based CHERISH (iii) adjustment to health state costs estimated by RWE survey, 2017 based on expert opinion; (iv) the inclusion of scoliosis assumptions aligned with clinical expert opinion; (v) the use of patient utilities from clinical advisors to Biogen; (vi) use of the adjusted "wide range" caregiver utilities and (vii) the inclusion of 2.5 caregivers supported by PAG surveys. Additionally, the later onset model also included a mortality adjustment factor (base case 0.75) for patients achieving type III milestones. All analyses were undertaken by assuming £75,000 nusinersen vial price and the commercial offer using the deterministic version of the revised cost-effectiveness model.

Additional sensitivity analyses were performed to explore: (i) a slower rate of HFMSE decline in RWC (ii) a range of type III mortality adjustments based on clinical expert opinion; ((iii) increases to age caps for improvement plateau in motor milestones; (iv) alternative assumptions to the proportion of patients who can worsen and improve in subsequent cycles; (v) alternative assumptions to the proportion of patients who discontinue therapy and following RWC transition matrix (vi) altering cost factors for RWE study 2017; (vii) patient utility sources and caregiver utility ranges, (viii) patient subgroups based on disease duration;

The methods used to implement these analyses in the early onset model are described below.

Exploratory analysis 1: Slower rate of decline in HFSME for the usual care arm

In this scenario, a mean monthly rate of HFMSE decline of 0.05 was used instead of [redacted] in the base case.

Exploratory analysis 2-3: Use of alternative mortality adjustment factors

In these scenarios, the type III mortality adjustment factor in varied at 0.5 and 1.

Exploratory analysis 4: Increases in age caps for improvement plateau

All health state improvement plateau ages are increased by 12 months excepted for the no milestones state

Exploratory analysis 5-6: Alternative assumptions regarding proportion of patients who worsen and can subsequently improve

Two additional scenarios were undertaken: (i) 9% of patients stop improving and follow RWC transition matrix, double that of the base case (ii) 2.25% of patients stop improving and follow RWC transition matrix, two times lower than in base case (except for discontinuation due to scoliosis surgery)

Exploratory analysis 7-8: Alternative assumptions to the proportion of patients who discontinue therapy and following RWC transition matrix

Two scenarios were explored: (i) Weighted average last 3 assessments (day 456, 365, and 274) as presented in Table 9; (ii) values in the base case doubled

Exploratory analysis 9: *Alternative assumptions regarding the loss of the ability to sit without support*

An analysis whereby patients do not lose the ability to sit without support and remain in the worst health state

Exploratory analysis 10: Alternative assumptions regarding health state costs

An analysis using a cost adjustment factor of 1 for type I.5 SMA was explored

Exploratory analysis 11: Alternative assumptions regarding patient utilities

One alternative analysis was undertaken to explore the impact of using different HRQoL estimates for patients with SMA: (i) analysis using utilities reported by the ERG clinical advisors

Exploratory analysis 12-13: Alternative assumptions regarding caregiver utilities

Two alternative analyses were assessed: i) using 'narrow range' estimates; ii) reducing the number of caregivers to 1 (type I caregivers for patient who lose ability to sit also reduced from 2.5 to 2)

Exploratory analysis 14-15: Patient subgroups based on disease duration

Two patient subgroups were examined based on the disease duration. Patient groups included those that had a disease duration < 25 months and > 25 months.

3.1.4 Results of the exploratory analyses – later onset SMA

The results of the company's base case and exploratory analyses are shown in Table 19 for £75,000 vial price and Table 20 for the commercial offer.

Base case scenario at £75,000 vial price has an ICER of £750,709 per QALY gained for patients and £323,663 per QALY gained including patient health gains and caregiver QALY losses. Respective numbers at the commercial offer are [redacted] per QALY gained for patients and [redacted] per QALY gained including the caregiver perspective. Application of the more optimistic assumption regarding later onset mortality, slightly reduces the ICER. Similarly, if the proportion of patients who worsen but then can subsequently improve is increased, the ICER increases, predominantly due to QALY losses for the patient and caregiver. If the last observed matrix for patients worsening is used, the ICER increases predominantly due to relatively great costs accrued vs QALYs gain; this particular scenario may be considered optimistic from the perspective that patients in the best two health states plateau and do not worsen (due to no worsening observations in CHERISH). Use of the ERG clinical advisor values marginally increases the ICER, predominantly due to high utility values for sits without support and no differentiation between any of the sitting health states. The model is most sensitive to health state costs and the age at which an improvement plateau is implemented, the inclusion of the ability to lose sitting without support and to the number of caregivers. If the cost adjustment applied to type I milestones (i.e. patients with type II losing the ability to sit over time), uses lower adjustment factors, increasing the ICERs. Similarly, if a lower caregiver number is assumed (2 for infantile onset and 1 for later onset), the ICER also increases. Similarly, removing the ability of patients to lose the milestone of sitting without support in both arms significantly increases the ICER due to significantly lower costs and higher QALYs being accrued in the RWC arm. In contrast, allowing an additional 12 months for before implementing the plateau cap significantly reduces the ICER as more patients attain higher milestones in the nusinersen arm.

Nusinersen is more cost-effective in a patient subgroup with shorter disease duration (<25 months, £522,740 and £232,859 at list price and [redacted] and [redacted] at the commercial offer for patients and patients plus caregivers, respectively), while the opposite stands for the group with longer disease duration (>=25 months). However, the latter subgroup should be interpreted with caution as this group was associated with a HFMSE decline of 0.0 during CHERISH which is highly unlikely to remain in the long-term and would go against the available literature and clinical expert opinion.

Table 19. Later onset model exploratory analyses, list price

Option	QALYs (patient)	QALYs (caregivers)	Cost	Inc. QALYs (patient)	Inc. QALYs (caregivers)	Inc. cost	ICER (patient)	ICER (patient+ caregivers)
Revised model base case								
Nusinersen	8.75	-9.02	£4,125,556	2.56	3.38	£1,922,784	£750,709	£323,663
RWC	6.19	-12.40	£2,202,772	-	-	-	-	-
S1 – Slower usual care arm decline in HFMSE								
Nusinersen	8.82	-8.89	£4,107,148	2.53	3.33	£1,930,041	£762,278	£329,352
RWC	6.29	-12.22	£2,177,107	-	-	-	-	-
S2 – Later onset mortality adjustment applied (0.5)								
Nusinersen	8.57	-9.02	£4,077,171	2.40	3.38	£1,876,198	£780,537	£324,474
RWC	6.17	-12.40	£2,200,973	-	-	-	-	-
S3 – Later onset mortality adjustment applied (1)								
Nusinersen	9.05	-9.03	£4,204,066	2.82	3.38	£1,999,262	£708,790	£322,409
RWC	6.22	-12.41	£2,204,804	-	-	-	-	-
S4 – Increases in ages for improvement plateau								
Nusinersen	10.39	-8.17	£4,144,630	4.19	4.24	£1,941,858	£463,155	£230,379
RWC	6.19	-12.40	£2,202,772	-	-	-	-	-
S5 – proportion of patients who can worsen and subsequently improve, doubled								
Nusinersen	8.65	-9.08	£4,123,978	2.46	3.32	£1,921,206	£782,226	£332,601
RWC	6.19	-12.40	£2,202,772	-	-	-	-	-
S6 – Proportion of patients who can worsen and subsequently improve, halved								
Nusinersen	8.81	-8.99	£4,126,322	2.62	3.41	£1,923,550	£735,546	£319,263
RWC	6.19	-12.40	£2,202,772	-	-	-	-	-
S7 – Proportion of patients who discontinue per cycle based on last observed assessment without adjustments								
Nusinersen	8.96	-8.74	£4,350,875	2.77	3.67	£2,148,104	£775,629	£333,830
RWC	6.19	-12.40	£2,202,772	-	-	-	-	-
S8 – Proportion of patients who discontinue per cycle doubled								
Nusinersen	8.45	-9.47	£3,771,463	2.26	2.93	£1,568,691	£693,656	£302,035
RWC	6.19	-12.40	£2,202,772	-	-	-	-	-
S9 – Patients do not lose the ability to sit without support								
Nusinersen	10.04	-6.35	£3,610,933	1.62	1.42	£2,300,240	£1,423,083	£757,520
RWC	8.43	-7.77	£1,310,693	-	-	-	-	-
S10 – Health state costs adjustment factor for type I (1.5)								

Nusinersen	8.75	-9.02	£3,886,876	2.56	3.38	£2,097,846	£819,058	£353,131
RWC	6.19	-12.40	£1,789,030	-	-	-	-	-
S11 – ERG clinical advisors' patient utilities								
Nusinersen	11.28	-9.02	£4,125,556	2.04	3.38	£1,922,784	£942,142	£354,739
RWC	9.24	-12.40	£2,202,772	-	-	-	-	-
S12 – 'Narrow range' caregiver utilities								
Nusinersen	8.75	-6.94	£4,125,556	2.56	2.05	£1,922,784	£750,709	£416,836
RWC	6.19	-9.00	£2,202,772	-	-	-	-	-
S13 – Number of caregivers 1								
Nusinersen	8.75	-5.39	£4,125,556	2.56	2.33	£1,922,784	£750,709	£392,735
RWC	6.19	-7.73	£2,202,772	-	-	-	-	-
S14 – Subgroup < 25 months disease duration								
Nusinersen	10.79	-6.78	£4,743,494	4.78	5.95	£2,497,798	£522,740	£232,859
RWC	6.01	-12.73	£2,245,696	-	-	-	-	-
S15 – Subgroup > 25 month disease duration [a]								
Nusinersen	8.23	-9.36	£3,798,352	0.73	1.07	£1,875,509	£2,572,819	£1,040,838
RWC	7.50	-10.44	£1,922,844	-	-	-	-	-

[a] mean change in HFMSE of 0.0 was observed in CHERISH which is highly unlikely to be sustained in the long term and would lack validity against the natural history literature

Table 20. Later onset model exploratory analyses, commercial offer

Option	QALYs (patient)	QALYs (caregivers)	Cost	Inc. QALYs (patient)	Inc. QALYs (caregivers)	Inc. cost	ICER (patient)	ICER (patient+ caregiver)
Revised model base case								
Nusinersen	8.75	-9.02	[redacted]	2.56	3.38	[redacted]	[redacted]	[redacted]
RWC	6.19	-12.40	[redacted]	-	-	-	-	-
S1 – Slower usual care arm decline in HFMSE								
Nusinersen	8.82	-8.89	[redacted]	2.53	3.33	[redacted]	[redacted]	[redacted]
RWC	6.29	-12.22	[redacted]	-	-	-	-	-
S2 – Later onset mortality adjustment applied (0.5)								
Nusinersen	8.57	-9.02	[redacted]	2.40	3.38	[redacted]	[redacted]	[redacted]
RWC	6.17	-12.40	[redacted]	-	-	-	-	-
S3 – Later onset mortality adjustment applied (1)								
Nusinersen	9.05	-9.03	[redacted]	2.82	3.38	[redacted]	[redacted]	[redacted]
RWC	6.22	-12.41	[redacted]	-	-	-	-	-
S4 – Increased ages for improvement plateau by 12 months (except worst health state)								
Nusinersen	10.39	-8.17	[redacted]	4.19	4.24	[redacted]	[redacted]	[redacted]
RWC	6.19	-12.40	[redacted]	-	-	-	-	-
S5 – Proportion of patients who can worsen and subsequently improve, doubled								
Nusinersen	8.65	-9.08	[redacted]	2.46	3.32	[redacted]	[redacted]	[redacted]
RWC	6.19	-12.40	[redacted]	-	-	-	-	-
S6 – Proportion of patients who can worsen and subsequently improve, halved								
Nusinersen	8.81	-8.99	[redacted]	2.62	3.41	[redacted]	[redacted]	[redacted]
RWC	6.19	-12.40	[redacted]	-	-	-	-	-
S7 – Proportion of patients who discontinue per cycle based on last observed assessment without adjustment								
Nusinersen	8.96	-8.74	[redacted]	2.77	3.67	[redacted]	[redacted]	[redacted]
RWC	6.19	-12.40	[redacted]	-	-	-	-	-
S8 – Proportion of patients who discontinue per cycle doubled								
Nusinersen	8.45	-9.47	[redacted]	2.26	2.93	[redacted]	[redacted]	[redacted]
RWC	6.19	-12.40	[redacted]	-	-	-	-	-
S9 – Health state costs adjustment factor for type I (1.5)								
Nusinersen	8.75	-9.02	[redacted]	2.56	3.38	[redacted]	[redacted]	[redacted]
RWC	6.19	-12.40	[redacted]	-	-	-	-	-
S10 – ERG clinical advisors' patient utilities								
Nusinersen	11.28	-9.02	[redacted]	2.04	3.38	[redacted]	[redacted]	[redacted]

RWC	9.24	-12.40	[redacted]	-	-	-	-	-
S11 – 'Narrow range' caregiver utilities								
Nusinersen	8.75	-6.94	[redacted]	2.56	2.05	[redacted]	[redacted]	[redacted]
RWC	6.19	-9.00	[redacted]	-	-	-	-	-
S12 – Number of caregivers 1								
Nusinersen	8.75	-5.39	[redacted]	2.56	2.33	[redacted]	[redacted]	[redacted]
RWC	6.19	-7.73	[redacted]	-	-	-	-	-
S13 – Subgroup < 25 months disease duration								
Nusinersen	10.79	-6.78	[redacted]	4.78	5.95	[redacted]	[redacted]	[redacted]
RWC	6.01	-12.73	[redacted]	-	-	-	-	-
S14 – Subgroup >25 months disease duration [a]								
Nusinersen	8.23	-9.36	[redacted]	0.73	1.07	[redacted]	[redacted]	[redacted]
RWC	7.50	-10.44	[redacted]	-	-	-	-	-

[a] mean change in HFMSE of 0.0 was observed in CHERISH which is highly unlikely to be sustained in the long term and would lack validity against the natural history literature

3.2 Conclusions

Nusinersen, an antisense oligonucleotide (ASO), is the first and only disease-modifying treatment for 5q SMA since the disease was first described. Nusinersen, a designated an orphan medicinal product by the EMA, is delivered intrathecally via lumbar puncture directly to the cerebrospinal fluid (CSF), a proven, targeted, and well tolerated route of administration. It increases levels of functional SMN protein, conferring improvements in motor function and survival, thereby changing the course of disease. Following the achievement of motor milestones and significant reduction in mortality in the pre-planned analyses, the phase III studies were stopped early and all patients in the sham-control arm were transitioned onto nusinersen in an extension study. In light of the high unmet need in SMA, nusinersen was recommended by the Committee for Medicinal Products for Human Use (CHMP) under accelerated assessment. Since EMA marketing authorisation in 2017, nusinersen has achieved reimbursement in 24 EU countries (and many more globally). In 2018, the innovative and life changing benefit of nusinersen was recognised in UK Prix Galien award where nusinersen won in the orphan medicine category (and nine other Prix Galien awards around the world) which included six other orphan medicines.

In this latest submission, Biogen has attempted to address the concerns raised by the committee from the previous meeting in October 2018. This has included undertaking a number of activities ranging from revising our commercial offer, revising assumptions in the cost-effectiveness model including available data from the SHINE extensions study data for infantile onset patients and conducting a series of validation exercises through patient advisory groups surveys and clinical expert meetings.

The results of these revisions suggest that nusinersen has the potential to be plausibility cost-effective in later onset SMA (type II/IIIa). These estimates, although higher than standard WTPs in some scenarios considered likely do not capture important benefits such as finer motor milestone attainment and attainment (compared to health states of gross milestones) which can have significant impacts on self-care and independence, in addition to broader societal costs to caregivers and families including loss of productivity. In contrast, it is highly unlikely to ever meet WTP under a STA for the infantile onset population, even at zero price, predominantly due to the high disease management costs accrued in the additional years of survival with nusinersen which are not offset with the predicted QALY gains.

Rationale for the results in this submission showing contrasting trends versus the original manufacturer submission is a result of several factors. In the original manufacturer submission, the key driver of higher ICERs in the later onset model versus the infantile onset model was the use of PedsQL utilities which showed little differentiation between the worse health state (e.g. *Sits without support but does not roll* [redacted] and W*alking unaided* [redacted]), whilst this was detrimental to the later onset model (few QALY gains), the additional survival accrued in the infantile onset model meant higher QALY gains for nusinersen, even for patients in the worst possible health state. The optimistic disease trajectory for nusinersen patients of continuous improvement post-trial follow-up (deemed clinically implausible) also contributed to the QALY gain which have since been revised with age caps, after which the attainment of higher gross motor milestones is not possible (based on clinical expert opinion). Another factor influencing the lower ICERs in the infantile onset model were the significantly underestimated disease management costs from Bastida et al., (2016) [11] which meant that additional years of survival did not accrue significant costs; these cost estimates have since been discredited by clinical experts and patient advisory groups and updated with cost sources and assumptions reflecting the rapidly evolving and increasingly interventional approach to standards of care. Furthermore, despite less optimistic disease trajectory assumptions in the later onset model, a key element of the natural history was not captured, whereby patients were not losing the ability to sit without support

over time. This leads to conservative estimates of costs and optimistic estimates QALYs accrued in the RWC arm.

Biogen appreciates the continued engagement by NICE and NHSE in this STA process. It was widely acknowledged that when assessing the first DMT in a rare disease, affecting primarily paediatric patients, it is challenging to truly evaluate the benefits to patients and whether these benefits translate into a good use of NHS resource under the current framework. The benefits of nusinersen go beyond factors considered under the STA process, and Biogen believes that in the light of this uncertainties and uncaptured benefits discussed above, nusinersen should be considered as a good use of the NHS resources.

4. References

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5. Appendix A – nusinersen transition probabilities

Presented below are the transition matrices applied in the nusinersen arm for:

- Baseline (Table 21)
- Day 64/ month 2 (Table 22)
- Day 183/ month 6 (Table 23)
- Day 302/ month 10 (Table 24)
- Day 394 / month 13 (Table 25)
- Day 578/ assumed month 18 (Table 26)
- Day 698 / assumed month 22 (Table 27)
- Day 818/ month 26 (Table 28)

Table 21: Health state distribution at baseline

No Miles.	Mild. Miles.	Mod Miles.	Sits w	Stands w	Walks w	S/W w/o	Dead
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 22. Transition probabilities Day 64 - Month 2

No Miles.	Mild. Miles.	Mod Miles.	Sits w	Stands w	Walks w	S/W w/o	Dead
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 23. Transition probabilities Day 183 - Month 6

No Miles.	Mild. Miles.	Mod Miles.	Sits w	Stands w	Walks w	S/W w/o	Dead
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 24. Transition probabilities Day 302 - Month 10

No Miles.	Mild. Miles.	Mod Miles.	Sits w	Stands w	Walks w	S/W w/o	Dead
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							

Table 25. Transition probabilities day 394 - month 13

No Miles.	Mild. Miles.	Mod Miles.	Sits w	Stands w	Walks w	S/W w/o	Dead
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							

Table 26. Transition probabilities Day 578 - assumed as month 18

No Miles.	Mild. Miles.	Mod Miles.	Sits w	Stands w	Walks w	S/W w/o	Dead
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							

[a] The base case assumes that after 13 months all patients in the No Milestone health state discontinue treatment. Hence patients do not improve.

Table 27. Transition probabilities Day 698 - assumed as month 22

No Miles.	Mild. Miles.	Mod Miles.	Sits w	Stands w	Walks w	S/W w/o	Dead
[redacted]							

[a] The base case assumes that after 13 months all patients in the No Milestone health state discontinue treatment. Hence patients do not improve.

Table 28. Transition probabilities Day 818 - Month 26

No Miles.	Mild. Miles.	Mod Miles.	Sits w	Stands w	Walks w	S/W w/o	Dead
[redacted]							

[a] The base case assumes that after 13 months all patients in the No Milestone health state discontinue treatment. Hence patients do not improve.

6. Appendix B – List of changes since previous submission

Table 29. Previous submission base case results

Previous submission base case	Infantile-onset ICERs (£ per QALY gained)	ICERs (£ per QALY gained)
Patient	895,865	394,343
Patient + Caregiver	684,389	174,106

6.1 Infantile onset model changes

6.1.1 S(t) T1 worksheet

1. Set previous Weibull parameters:

Table 30. Weibull parameters in previous submission

Previous submission ("S(t) T1" sheet BL12:BM13)	Nusinersen (Weibull)	RWC (Weibull)
Rate	88.9517	23.8970
Shape	0.7716	0.7716

Table 31. Weibull parameters in new submission

New parameters ("S(t) T1" sheet BG12:BH13)	Nusinersen - SHINE (Weibull)	RWC (stratified Weibull)[a]
Rate	204.2949	22.7949
Shape	0.6112	0.8087

[a] The stratified Weibull was used as it fitted each arm separately.

6.1.2 Efficacy T1 worksheet

2. Select the Weibull function from the dropdown in row 20.
3. Don't apply the factor for dropdown in row 100.
4. Set the taper period to 60 months (Cell I90)
5. Set the end of the end of the trial to 13 months:
    a. Set it in Efficacy T1 I86:J86
    b. Set it in Efficacy T1 I53:J53
    c. Set it in Efficacy T1 I116:J122
6. Set the percentage plateauing to 1% (in I127:I132)
7. Set the percentage worsening from those plateauing to 100% (in I138:I144)
8. Set I157 to 0% (% of patients worsening among patients receiving nusinersen)
9. Set Nusinersen rate of increase (dropdown row 150) to option 1 "ENDEAR baseline day 0 to day 394"

6.1.3 Costs T1 worksheet

10. Set vial cost to 75,000
11. Set number of paid loading doses to 4 (dropdown row 18)

12. Dropdown row 26 set it to Don't apply rebate
13. Update costs per type of care

Table 32. Health state costs by type. RWE survey 2017 [12]

	RWE survey (Previous submission) [12]
Type I (F143, F150)	77,968
Type II (I143, I150)	55,185
Type III (L143, L150)	20,229

6.1.4 Utility T1 worksheet

14. Set patient utility values to EQ-5D vignette study (dropdown row 11)
15. Update number of caregivers to 2.

6.1.5 Markov Nusinersen T1 worksheet

The Markov sheet needs to be updated to reflect the ENDEAR data instead of the SHINE data.

16. Copy values from previous submission model and paste them in the new model:
    a. Copy F20:N24 and paste as values in F20:N24
    b. Copy AD24:QP28 and paste as values in AD24:QP28
17. Update formulas in the new version
    a. Copy F29:N29 and paste formulas in F25:N28
    b. Copy T29:AA29 and paste formulas in T25:AA28
    c. Copy QR29:RC29 and paste formulas in QR25:RC28
    d. Copy UP29:UU29 and paste formulas in UP25:UP28

6.1.6 Markov RWC T1 worksheet

18. Copy values from previous submission model and paste them in the new model:
19. Copy F20:M20 and paste as values in F20:M20

6.2 Later onset model changes

6.2.1 Efficacy T2 worksheet sheet

1. Set % of patients having scoliosis surgery to 60% (Cell F43 and I43)
2. Set year after which patients have scoliosis surgery in the nusinersen arm to 12 and 15 years (Cells F47 and F50, respectively)
3. Set year after which patients have scoliosis surgery in the RWC arm to 10 and 15 years (Cells I47 and I50, respectively)
4. Set mortality adjustment factor to Don't apply (dropdown row 82)
5. Set the month at which patients start plateauing to 15 (I98:I103)
6. Set the % plateauing to 1% (I119:I123)
7. Set the % worsening from those plateauing to 100% (in I119:I123)
8. Set extrapolation method for patients losing ability to sit to "Patients do not lose ability to sit" (dropdown row 127)
9. Set the % of patients worsening among patients receiving nusinersen to 0% (I144)

6.2.2 Costs T2 worksheet

10. Set vial cost to 75,000
11. Set number of paid loading doses to 4 (dropdown row 18)
12. Dropdown row 26 set it to Don't apply rebate
13. Update costs per type of care (see type II, III estimates as per Table 32)

6.2.3 Utility T2 worksheet

14. Set patient utility values to EQ-5D vignette study (dropdown row 11)
15. Set the caregiver utilities to the "wide range" values in the previous submission model
16. Update number of caregivers to 2.

Table 33. 'Wide range' caregiver values used in the previous submission

Later onset health state	Utility estimate
Sits without support but does not roll	0.484
Stabilization of Baseline Function	0.592
Sits and crawls with hands and knees	0.700
Stands/Walks with assistance	0.807
Stands unaided	0.915
Walks unaided	0.915

6.2.4 Default T2 worksheet

17. Cell G636: =J818
18. Cell H637 = J819

6.2.5 Markov RWC T2 worksheet

19. There was an error in the formula estimating the caregiver QALYs in the Markov RWC T2 sheet which has been corrected (Column CK:CS). This resulted in slightly different caregiver QALYs. To replicate the same result as in the previous submission model, the values from CL20:CS322 can be pasted in the new model in CL20:CS322

7. Appendix C - RWE survey

This appendix outlines a brief overview from a survey conducted in September 2017 to understand the real-world perspectives of UK paediatric neuromuscular disease centres. Further details are available in the accompanying report.

Key objectives of the research were to understand:

- Burden of illness (understand the disease burden in the UK context)
- UK epidemiology (establish prevalence, split by type and share across key centres)
- Resource utilisation (establish key drivers of resource use in diagnosis and treatment)
- Patient pathway (understand the progression of disease and the time to key events /milestones.

7.1 Methodology

7.1.1 Questionnaire

A questionnaire was developed to enable online collection of current patient and treatment practice data from paediatric neuromuscular disease (NMD) treatment centres, in the areas of epidemiology, disease progression and resource utilisation. A process was then initiated to validate the survey in terms of relevance and completeness of questions from the perspective of UK treatment practice. This came in the form of two parts: an advisory board (held on 11th September 2017) and a meeting with one of the lead NMD consultants at Great Ormond Street Hospital (GOSH) in London (held on 27th July 2017).

7.1.2 Recruitment

A convenience sample of nine paediatric NMD centres was recruited across the UK from the following regions:

- England (London): GOSH and Evelina
- England (Outside London): Leeds, Newcastle and Oswestry
- Scotland: Dundee and Glasgow
- Northern Ireland: Belfast
- Wales: Cardiff.

7.1.3 Analysis

Analysis was conducted at a centre level, with regional and UK perspectives generated using weighted averages (according to relative patient population at each treatment centre) for questions related to patients (e.g. proportion of patients receiving a particular intervention). Where questions related to treatment centres (e.g. proportion of centres using a particular monitoring methodology), averages were not weighted by patient numbers. In the survey, participants were asked to indicate where they were unable to answer a question. Where this was the case (or where no answer was provided), these centres were excluded from the analysis for that particular question/part of question.

7.1.4 Cost analysis

An analysis was also conducted which converted units of resource usage into annual per patient costs. Due to a lack of standardised treatment guidance in this area, the unit costs used for conversion were gathered

from a range of sources. These unit costs were sense-checked against those used in other studies (e.g. Bastida).

Table 34. Case loads by centre

	Number of patients			Total
	SMA I	SMA II	SMA III	
GOSH				
Evelina				
Oswestry				
Leeds				
Newcastle				
Glasgow				
Dundee				
Cardiff				
Belfast				
Total UK				
Scotland				
England & Wales				
England & Wales (excl. London)				
London				

The centres located in London (GOSH & Evelina) treat the largest group of SMA patients ( ) with GOSH holding the largest number of all centres ( ), followed by Newcastle (and Oswestry (. The Welsh, Northern Irish and Scottish centres treat the fewest patients; ((and (respectively.

It should be noted that the proportion of patients of each type was not consistent across all treatment centres. Comparatively low levels of type III patients were reported in Cardiff and Belfast, while no type III patients were reported at Glasgow. Comparatively low levels of type I patients were seen at Newcastle, with none reported at Dundee. Across the treatment centres, type II patients were consistently the most prevalent subgroup.

8. Appendix D- Patient advisory group surveys

The impact of SMA on patient community and caregivers is substantial, in terms of physical, psychological and financial strain. SMA UK, previously known as the SMA Support, conducted a survey in January 2018 with patients and caregivers affected by SMA to contextualise and substantiate the impact of the disease on SMA community. The survey explored health impact of SMA on children, young people and adults with the condition who have not been treated with nusinersen and management of the disease. To extend and validate these observations a second survey on behalf of Biogen was conducted in December 2018 including patients both treated and not treated with nusinersen and their unpaid carers. The follow up survey completed by caregivers, additionally explored productivity and financial implications of unpaid carers of patients with SMA.

The findings of these surveys are used to validate assumptions used in the NICE appraisal process of nusinersen, such as direct costs of disease management, caregiver burden and other costs that fall outside of the health care system, but still affect everyday life of patients and carers affected by the disease.

The data from 125 respondents from the initial survey (type II and type III) and 188 respondents from the follow up survey (all disease types) were analysed to obtain population averages and results stratified by disease types.

8.1 Disease management costs

The cost of SMA to the healthcare system is significant. However, there have been numerous challenges in accurately depicting the true cost of this orphan disease. As is evident from the conducted surveys and feedback from PAGs during the second AC meeting, substantial hidden costs to families and caregivers remain uncaptured. Furthermore, patient experts at the committee meeting in June in addition to clinical advisors to the ERG noted that the health state costs sourced from Bastida et al. (2016) [11] were significantly underestimated, especially for type I & type II SMA.

The treatment paradigm for SMA is changing with treatments such as nusinersen, partly due to changing societal expectations and greater empowerment of patients and families in clinical decision making [13]. New standard of care includes more aggressive screening for hypoventilation and impaired airway clearance with proactive treatment earlier in course of the disease, which will increase direct disease management costs [13]. This will result with most severe patients living longer, but likely to be dependent on non-invasive and invasive support.

The SMA patients have frequent contact with various health professionals and may experience several episodes of costly unplanned admissions due to high disease burden. As per the SMA UK survey results, the mean number of NHS funded health interventions (elective, semi-elective and nonelective interventions) used by SMA patients was 6.96 (type II 8.7 interventions and type III 4.27 interventions). The mean number of health interventions which were required by an SMA patient but were not currently in place was 1.88 (type II 2.61 interventions and type III 0.76 interventions).

In addition to numerous, often unplanned, health interventions there is also a requirement for SMA patients to have contact with health care professionals (HCPs) e.g. consultants, physiotherapists, occupational therapists, orthotists, wheelchair specialists, general practitioners (GPs), social workers or nurses. Findings from the SMA UK survey suggest that in the last 12 months before survey completion, the largest proportion of patients (36.8%) saw between 0-5 different HCPs.

Using the data from the first survey, average annual NHS costs of treating SMA patients were calculated and split by disease type (Table 35). These estimates do not include the costs of unplanned admissions. Results are based on the average SMA type II patient requiring 8 hours of care in a 24hr period and an SMA type III patient requiring 4 hours in the same period. Analysis shows that the total average annual cost to the NHS and Personal Social Services (PSS) is £49,593. Care costs would most likely be borne

by the local authorities. Planned interventions, drugs and equipment for the average SMA patient are estimated to cost £6,944.

Table 35. Average annual NHS costs associated with SMA

	Annual NHS cost per SMA patient	SMA type II patient	SMA type III patient
Interventions, drugs and equipment	£6,363	£4,852	£1,511
Care	£42,648	£53,086	£26,674
Total average annual cost per patient	**£49,013**	**£57,938**	**£28,185**

Results from the follow up survey suggest that over a 12-month period an SMA patient was seen most frequently to have >10 planned appointments with a significant number of SMA patients experiencing unplanned appointments (Table 36). In addition to this the majority of SMA patients experienced >10 additional issues (sudden ill health, equipment breakdown etc) related to SMA.

Table 36. SMA-related medical events by disease type

Medical appointments	Type I SMA patient	Type II SMA patient	Type III SMA patient	Types II and III SMA patients
Planned appointments >10 (%)	35.00%	34.18%	12.20%	26.67%
Unplanned appointments	83.33%	70.00%	60.53%	66.67%
Other SMA-related issues	90.48%	79.01%	78.05%	78.69%

8.2 Caregiver burden

Carer impacts are not explicitly part of the NICE reference case but can be taken into account where they are considered to be important. SMA patients often require help with daily living tasks including washing, dressing, toileting, transfers, eating and drinking, preparing meals and other tasks. A lion share of assistance to SMA patients is provided by unpaid carers, so their everyday lives are heavily impacted by the disease. Due to the complexity of the condition, informal carers have to devote substantial time and often money to take care of a patient with SMA. Follow up survey conducted on the behalf of Biogen, gave an insight into the caregiver burden associated with care for SMA patients.

Nusinersen had been used to treat 28 out of the 188 respondents and of these 28 people, 50% experienced a reduction in their care requirements, 39% of the care requirements remained the same and 11% experienced an increase in care requirements (see Table 37).

Table 37. The impact of nusinersen on care requirements

If currently treated with nusinersen, what has been the impact on their care requirements?	Frequency N=28	% of treated population N=28
Increased	3	11%
Decreased	14	50%
Stayed the same	11	39%

The mean number of people involved in an SMA patients' care each week was 2.64 (n=187). SMA patients had a variety of different people providing unpaid care for them, respondents most frequently had parents as their carers followed by grandparents. Mothers spent a mean of 71.46 hours performing care and fathers spent a mean of 43.34 hours, grandparents spent a mean of 15.05 hours caring. Partners of SMA patients spent a mean number of 52.31 hours (Table 38).

Table 38. Average number of hours per week spent caring for the patient with SMA

Caregiver	N	Mean	SD
Mother	148	71.46	53.91
Father	125	43.34	43.62
Partner of person with SMA	26	52.31	43.39
Siblings of person with SMA	59	20.30	35.58
Grandparents of person with SMA	61	15.05	14.79
Other relatives	24	14.92	15.39
Friends	29	9.48	9.14
Neighbors	6	3.33	3.44
Other: Please specify	7	69.57	71.18

Table 39 shows the reduced working hours from unpaid careers stratified by disease type. As type I patients have the greatest care needs, the number of reduced hours is the highest for this patient group.

Table 39. Reduced working hours per week by unpaid caregiver and type

Average number of hours per week: Caregiver	N	Mean	SD
Type I			
Mother	28	88.29	54.45
Father	28	52.52	50.55
Partner of person with SMA	0	-	-
Siblings of person with SMA	6	11	7.75
Grandparents of person with SMA	11	17.27	20.24
Other relatives	5	11.6	9.61
Friends	2	5	0
Neighbors	0	-	-
Other: Please specify	1	17	0
Type II			
Mother	91	76.06	54.36
Father	74	47.87	43.53
Partner of person with SMA	11	45.82	21.9
Siblings of person with SMA	35	25.76	43.48
Grandparents of person with SMA	39	15.38	12.04
Other relatives	13	17.08	17.75
Friends	16	12.19	10.38
Neighbors	2	2.5	2.12
Other: Please specify	4	105	77.86
Type III			
Mother	29	40.79	39.65
Father	23	17.57	20.68
Partner of person with SMA	15	57.07	54.43
Siblings of person with SMA	18	12.78	19.22
Grandparents of person with SMA	11	11.64	18.25
Other relatives	6	13	15.23
Friends	11	6.36	6.79
Neighbors	4	3.75	4.19
Other: Please specify	2	25	21.21
Types II and III			
Mother	120	67.54	53.24
Father	97	40.69	41.31
Partner of person with SMA	26	52.31	43.39
Siblings of person with SMA	52	21.34	37.35

Grandparents of person with SMA	50	14.56	13.52
Other relatives	19	15.79	16.68
Friends	27	9.81	9.4
Neighbors	6	3.33	3.44
Other: Please specify	6	78.33	73.72

The number of unpaid caregivers differs by disease type (Table 40). Respondents indicated that for every SMA person a mean of 2.82 caregivers is utilised for type I, a mean of 2.80 for type II and a mean of 2.22 for type III.

Table 40. Unpaid number of caregivers per week

Unpaid care per week	N	Mean	SD
Type I	28	2.82	1.25
Type II	108	2.8	2.31
Type III	51	2.22	1.38
Types II and III	159	2.61	2.07

8.3 Employment implications and productivity loss

A high proportion of working parents (71%) of patients with SMA had to reduce their hours or even leave their jobs, leading to financial strain and further impacting on their quality of life (Table 41). 49% of carers (87/177 respondents) had to give up work completely. In fact, as per survey findings the employment implications of the disease often affect more than one carer. On average across all SMA types, 1.47 carers had to reduce their working hours. Table 42 shows caregivers' reduced hours per disease type. As expected, due to highest disease burden, caregivers of patients with type I SMA had the highest number of reduced working hours per week.

Many unpaid caregivers reported being required to refuse promotion and change their career goals, 109 out of 174 (63%). This was true for 74% of type I caregivers, 65% of type II caregivers and 51% of type III caregivers. Of those in part-time or full-time work, over the last 12 months work had to be missed for either planned appointments, unplanned appointments and/or other SMA-related issues.

Table 41. Average number of hours reduced per week

Average number of hours per week: Caregiver	N	Mean	SD
Mother	94	29.43	11.33
Father	38	18.13	12.31
Partner of person with SMA	10	24.25	15.23
Siblings of person with SMA	4	18.63	12.75
Grandparents of person with SMA	12	16.75	11.60
Other relatives	0	-	-
Friends	0	-	-
Neighbors	0	-	-
Other: Please specify	2	20.25	6.72

Table 42. Average number of hours reduced per week per disease type

Average number of hours per week: Care-giver	N	Mean	SD
Type I			
Mother	24	33.35	8.45
Father	13	20.04	12.77
Partner of person with SMA	0	-	-
Siblings of person with SMA	0	-	-
Grandparents of person with SMA	2	23	1.41
Other relatives	0	-	-
Friends	0	-	-
Neighbors	0	-	-
Other: Please specify	1	25	0
Type II			
Mother	56	28.71	11.6
Father	19	17.39	12.74
Partner of person with SMA	3	30.83	23.23
Siblings of person with SMA	3	19.83	15.33
Grandparents of person with SMA	9	13.06	10.28
Other relatives	0	-	-
Friends	0	-	-
Neighbors	0	-	-
Other: Please specify	1	15.5	0
Type III			
Mother	14	25.61	13.29
Father	6	16.33	11.41
Partner of person with SMA	7	21.43	11.71
Siblings of person with SMA	1	15	0
Grandparents of person with SMA	1	37.5	0
Other relatives	0	-	-
Friends	0	-	-
Neighbors	0	-	-
Other: Please specify	0	-	-
Types II & III			
Mother	70	28.09	11.92
Father	25	17.14	12.21
Partner of person with SMA	10	24.25	15.23
Siblings of person with SMA	4	18.63	12.75
Grandparents of person with SMA	10	15.5	12.4
Other relatives	0	-	-
Friends	0	-	-
Neighbors	0	-	-
Other: Please specify	1	15.5	0

In the event of an informal carer being required to reduce their work hours or give up work entirely there is an associated loss of productivity. The requirement for the unpaid caregiver to give up work represents a loss of household income. In the initial survey, 43 unpaid assistants to type II patients were required to give up work completely and 25 were required to switch to part-time hours. For unpaid caregivers to type III patients, 14 were required to give up full-time work completely and 12 were required to reduce their hours to part-time. This represents an annual loss of productivity of £19,422 per unpaid caregiver who gives up full-time work and £10,883 per unpaid caregiver who reduces their working hours to part-time (Table 43). This was calculated using the human capital approach, adjusting lost salaries by average labour force participation and rate of unemployment.

Table 43. Annual Loss of productivity per unpaid caregiver using the human capital approach – results from the SMA UK survey

		Unpaid caregiver (N)	
Working hours	**Lost annual productivity per unpaid caregiver**	**Type II SMA patient**	**Type III SMA patient**
Given up full time	£19,422	43	14
Reduced to part time	£10,883	25	12
Totals		**68**	**26**

A data from the follow up survey were also used to calculate the loss of productivity associated with caring for SMA patient (Table 44). The value of annual lost productivity per unpaid caregiver is estimated to be £16,958, for the follow up survey population.

Table 44. Value of annual productivity loss per caregiver

Human capital productivity loss	Average number of full-time employment is reduced by hours reduced	Average hourly rate	Mean weekly loss of production cost per patient	Value of average lost annual productivity per unpaid caregiver
Across all caregivers	25.08	£13.00	£326	£16,958

Estimates from both surveys are aligned, given the number of hours that full-time work is reduced by, roughly half way between giving up work and going part-time. Follow up survey recorded the effect of nusinersen on the care requirements for an SMA patient and noted that 50% of those that were receiving nusinersen experienced a reduction in their care requirements. This shows the potential effect that nusinersen could have on the caregivers. A reduction in care burden could potentially enable an increase in working hours and therefore the ability to earn more money and pursue some of their career goals.

8.4 Out of pocket expenses

Caregivers in addition to having to give up work can be faced with very significant OOP costs (Table 45). From 136 respondents from the follow up survey the mean cost for travel, parking and overnight stays for both the caregiver and SMA patient was £71.96 per each appointment. Also, caring for an SMA patients is complex and may require additional equipment or home adjustments, not typically covered by insurance. Table 46 outlines the most expensive items that an SMA patient may need, they may not be covered by the statutory health insurance. The wheelchair accessible vehicle is the costliest health intervention, with a mean cost of £18,139.

Table 45. Money spent on travel and accommodation

Money spent on travel and accommodation	N	Mean	SD
Type I	7	103.57	90.86
Type II	39	68.38	57.32
Type III	30	69.23	55.55
Types II and III	60	68.75	56.14

Table 46. Significant out of pocket costs for family with SMA patient

Equipment	Mean
Standing frame	£4,288
Specialist car seat	£1,297
Powered wheelchair	£17,893
Assisted cough (e.g. cough assist machine)	£3,800
Day time non-invasive ventilation	£3,000
Night time non-invasive ventilation	£4,520
Wheelchair accessible vehicle	£18,139
Hoist (mobile or ceiling track)	£7,361
Home adaptations to bedroom	£14,069
Home adaptations to toilet and bathroom facilities	£7,111
Home adaptations to the kitchen	£6,114
Other home adaptations (none of the above can be listed again)	£13,988
Other	£9,081

According to the findings of the SMA Support survey, the annual potential OOP cost to unpaid caregivers and SMA patients for interventions, drugs and equipment is thought to be £6,363, the cost of care (based on required average of 6.5 paid care hours per 24-hour period from survey A at £18 per hour) is estimated to be £42,649, giving a potential total annual OOP of £49,012 (Table 47).

Table 47. Annual potential OOP costs – results based on the SMA UK survey

	Annual potential caregiver OOP cost per average patient	Type II SMA patient	Type III SMA patient
Interventions (including drugs and equipment)	£6,363	£7,981	£3,855
Formal care	£42,649	£53,086	£26,674
Total average annual cost per patient	£49,012	£61,066	£30,529

Based on the survey results conducted on the behalf of Biogen, the average annual OOP cost was £5,362.93, £8,005.55 and £6,979.73 for type I, II and III SMA patient respectively. Type II patients are associated with a higher resource use than type I or type III patients, as they used more expensive health interventions such as powered wheelchairs, wheelchair accessible vehicles, specialist bed hoist and home adaptations which tend to be more costly.

Table 48. Annual potential OOP on interventions and appointments – results based on the follow up survey

	Type I SMA patient	Type II SMA patient	Type III SMA patient
Interventions (including drugs and equipment)	£5,259.36	£7,937.17	£6,910.50
Medical appointments (including travel and overnight stay)	£103.57	£68.38	£69.23
Total average annual cost per patient	£5,362.93	£8,005.55	£6,979.73

8.5 Travel time

Travelling is a necessary requirement for SMA patients for their appointments or buying or repairing equipment. Most frequently, the respondents recorded that their specialist SMA hospital was <2 hours away (32%), but some patients recorded having to travel for as long as 4 hours (3%) (Table 49). Local appointments were most frequently <30 minutes travelling (42%) but some respondents recorded travelling up to 3 hours (3%) (Table 50). The travelling to these various appointments with the SMA patient has an associated OOP expense to the caregiver and SMA patient, but also impacts caregiver's productivity and overall quality of life.

Table 49. Travelling time to SMA specialist hospital

How far is the person with SMA's specialist hospital for SMA in terms of travel time?	Frequency	(%)
<15 minutes	3	2%
<30 minutes	25	16%
<1 hour	47	30%
<2 hours	51	32%
<3 hours	24	15%
<4 hours	5	3%
≥4 hours	4	3%

Table 50. Travelling time to local SMA related appointments

If other appointments are attended locally, how far are the person with SMA's local appointments for SMA in terms of travel time?	Frequency	(%)
<15 minutes	17	11%
<30 minutes	66	42%
<1 hour	53	33%
<2 hours	11	7%
<3 hours	4	3%
<4 hours	0	0%
≥4 hours	0	0%
Not applicable	8	5%

9. Appendix E – Base case settings & validation tests

Table 51. Summary of revised economic model assumptions for infantile and later onset models

Model component / parameter	Biogen's base case models submitted to second AC meeting	ERG comment / Clinical validation	Biogen's new base case models
Early onset SMA mortality risk	Weibull model with HR tapered over 60 months and no mortality adjustment to nusinersen-treated patients in the better health states	ERG noted that estimated lifetime survival benefit of nusinersen versus BSC was more conservative approach than the company's original base case model. Despite that, clinicians considered a taper of the HR over 60 months as pessimistic. Also, patients achieving type II milestones have a survival closer to type II (factor of 0.75), since none of the patients sitting without support or with a higher milestone died during ENDEAR or SHINE. Clinical opinion considered the factor to be between 0.5 and 1.0.	The base case was updated to include a taper period over 120 months and mortality adjustment factor of 0.75.
Early onset transition matrices within clinical trial	Using transitions observed in ENDEAR trial	The long-term benefits of nusinersen are uncertain.	The transition matrices for the nusinersen arm of the infantile onset model were updated with data from SHINE. The patient counts from baseline to day 394 were updated and new assessment points were included (day 578, 698, 818, and 938). The transition matrix based on the last assessment at day 938 was not used due to the low number of patients that had reached this timepoint (N=5).
Transition matrices post clinical trial follow up	Model allowed a specified proportion of patients to reach an improvement plateau post month 13/15 and either remain in the same health state (plateau) or follow the trajectory of the usual care arm.	No patients ware assumed to plateau, hence sub-model for those reaching a plateau was deemed redundant in the company's base case models.	After trial follow-up the model assumes that patients reach an improvement plateau at a defined month, and that a proportion of those patients reaching an improvement plateau progress/worsen as in the RWC arm. Before reaching the improvement, plateau patients will continue to improve based on the CHOP-INTEND/HFMSE rate of change. Treatment discontinuation is applied to all patients in the No milestone health state after 13/15 months, and to patients who worsen after reaching an improvement plateau

Trajectory of patients that keep improving in the model	Model allowed that patients can remain on the same health state or move to the next best health state.	Not commented on	For the group of patients improving according to the transition matrix estimated from the rate of CHOP INTEND/HFMSE score increase, we have added an additional input which assumes that a proportion of patients receiving treatment are also allowed to worsen, but with the possibility to improve at a later time point as the patients remain on treatment. In early onset mode, the rate of CHOP INTEND score change was also updated to reflect SHINE data. The percentage of patients worsening who could still improve was based on a weighted average of patients improving after they had worsened in the previous assessment.
Trajectory of patients reaching an improvement plateau	The model allowed for a proportion of patients to reach a plateau, but 100% of these patients were assumed to worsen.	No patients ware assumed to plateau, hence sub-model for those reaching a plateau was deemed redundant in the company's base case models.	For the early onset model, the base case assumes that patients in the *Mild milestones*, *Moderate milestones* and the *Sits without support* health states reach an improvement plateau at 53 months in the model (i.e. 59 months of age; [mean age entering the model: 5.6 months]); and patients in the *Stands with assistance* and higher health states reach an improvement plateau at 63 months in the model (i.e. 69 months of age). For the later onset model, the base case assumes that patients in the *Sits without support but does not roll*, *Sits and rolls independently*, and S*its and crawls with hands and knees* health states reach an improvement plateau at 15 months in the model (i.e. 59 months of age; [mean age entering the model: 44 months]); and patients in the stands/walks with assistance and higher health states reach an improvement plateau at 25 months in the model (i.e. 69 months of age). Patients in the *Sits without support but does not roll* health state are assumed to all discontinue treatment after trial follow-up and follow the RWC transition matrix

Patients worsening out of those that reach an improvement plateau	In the previous model all patients assumed to reaching a plateau would worsen. 1% of patients assumed to lose efficacy and discontinue during each model cycle; these patients never regain milestones.	Some proportion of patients are likely to lose milestones or plateau and previous assumption was not supported by data. No patients reached the best health states in ENDEAR or CHERISH.	To determine the percentage of patients worsening from each health state we estimated a weighted average of the proportion of patients worsening at each assessment in ENDEAR+SHINE/CHERISH. Worsening is assumed to be health state specific. The percentage of patients worsening was estimated at the last assessment in the later onset model (transition matrix at day 456; based on CHERISH data). The later onset proportions were selected for consistency with the later onset model. It is worth noting that SHINE data did not show any patient worsening compared to their day 394 assessment (only 6 patients lost milestones after day 394 [1 at day 578, 3 at day 698, and 1 at day 938]; however, their overall trajectory was either maintain milestone [5] or improve milestone [1] compared with the milestone at day 394. Patients discontinuing treatment assume same risk of death as patients in the RWC arm.
Additional scenario to account for patients with type II SMA losing the ability to sit	Not incorporated in previous version	Not commented on by the ERG, although consulted clinicians considered that to be important especially when modelled over a life time horizon and is reflect-ed in the natural history literature.	Given the time constraints and model complexity, we elected not to introduce a new health state in the later onset model for the losing the ability to sit. The model therefore applies the proportion of patients losing the ability to sit to those patients in the *Sits without support but does not roll* health state and calculates the QALYs and health states costs using a weighted average based on the *Sits without support but does not roll* health state utility and the *moderate milestone* infantile-onset health state utility, caregiver number and disutility, in addition to the type II and type I health state costs.
Survival in the later onset model	Model did not include mortality adjustment factor.	ERG noted that mortality adjustment yields in optimistic results. Consulted clinicians believed it was appropriate to include a mortality adjustment for patients achieving type III milestones of standing/walking unaided with a range between 0.5 – 1.0.	Patients achieving type III milestones have a survival closer to the general population (factor of 0.75).

Health state costs	RWE survey (2017) [12] informed costs per average SMA patient. The total cost for a typical patient per year was estimated to be £77,968 for type I, £58,185 for type II and £20,230 for type III.	The costs from the survey are considerably higher than the estimates in the original company submission and the methods used for these costs have not been presented in detail. All clinicians consulted noted that the trend in costs from the survey were appropriate (highest cost in type I, followed by type II and type III accruing the lowest cost). However, all clinicians expected the costs for type I to be higher than estimated driven by more costs accrued in major clinical interventions (closer to a factor of 2 which was also supported by PAGs at the committee discussions in October).	As per feedback from clinicians, only GOSH and Newcastle were used in the weighted average for the health state costs (covering [redacted] of patients in the survey). A cost factor of 2 was applied to type I patients. The costs were assumed as follows: £148,214, £68,322 and £21,765 for type I, II and III SMA patients respectively.
Patient utilities	Based on Lloyd et al. (2017) [15] EQ-5D vignette study.	As noted by the ERG report, none of the available sources for patient utilities are ideal; the Lloyd et al. (2017) [15] study was selected for inclusion in the ERG-preferred analysis as this broadly aligned with the health states used in the company's models and health states were valued using the EQ-5D. The clinical experts consulted were asked to comment on the appropriateness of these sources and concluded that the midpoints between ERG clinical adviser estimates and case vignette values are more appropriate.	As per feedback from clinicians. It should be noted that both the ERG and Biogen estimates are non-preference based estimates of HRQoL despite better validity.
Caregiver utilities	Assumes best health state is associated with general population utility; worst state is associated with mean caregiver utility in Bastida et al (2017.) [14]; equal difference in utility assumed between adjacent states. The only exception is	ERG noted that appropriate data to estimate caregiver utilities is lacking.	The lower and upper bounds of the caregiver's utility values for both the early and the later onset model have been calculated using the similar approach, as in previous submission, with an additional assumption that utility value of the *Sits without support* from the early onset model is equivalent to utility value of the *Sits without support but does not roll* from the later onset model.

	that the same caregiver utility is applied for the ‘stands unaided’ and ‘walks unaided’ states in the later onset SMA model.		
Number of caregivers	2 caregivers for both the early and later onset model	ERG noted that it might be reasonable to include health losses for more than one caregiver, although that has a significant impact on the ICER for nusinersen (favourable impact on the ICER for one population, but a negative impact on the other). The revised assumption is supported by the surveys conducted by the SMA UK and Biogen	3 caregivers for infantile onset and 2 caregivers for later onset SMA.

Table 52. Validation tests

Test	Expected effect	Infantile-onset model	Later onset model
1. Set scoliosis surgery probability equal to zero	No patient should enter sub-models 4,5,6 or 7 post-scoliosis surgery sub-models)	Model behaves as expected	Model behaves as expected
2. Set discontinuation probability equal to 1.0	All patients should immediately leave sub-model 1	Model behaves as expected	Model behaves as expected
3. Set discontinuation probability equal to zero (including those with no milestones) and scoliosis surgery probability equal to zero	No patient should enter sub-models 2,3,4,5,6 or 7 (all patients remain "improvers" until death)	Model behaves as expected	Model behaves as expected
4. Set discontinuation probability equal to one (including those with no milestone) and scoliosis surgery probability equal to one	No patient should enter sub-models 1 or 2 some should move to post-scoliosis surgery sub-models	Model behaves as expected	Model behaves as expected

10. Appendix F – Nusinersen Access By Country

Table 53. Access & Reimbursement Details by Country

Access & Reimbursement Details by Country	
Austria	Reimbursed access - in line with the label - 5q spinal muscular atrophy (SMA)
Belgium	Reimbursed access in line with the label - 5q spinal muscular atrophy (SMA) effective September 1st - inclusion/ exclusion criteria may apply
Bulgaria	Partner in place; preparing for reimbursement dossier submission
Canada **INESSS and the Government of Quebec**	Interim agreement with pCPA. The Provinces will cover limited number of Type 1 SMA patients (according to the current HTA recommendations) and Biogen Canada will cover the most urgent Type 2 and 3 patients – defined as those with the highest risk of losing motor function. Final reimbursement criteria to be defined in January 2019, once the Canadian Agency for Drugs and Technologies in Health (CADTH) provide their final assessment, following Biogen's resubmission in September 2018. Reimbursed Access - pre-symptomatic and symptomatic patients with Type 1, 2 and 3 of all ages
Croatia	Reimbursed Access -Type I, II, III (<18 yrs.)
Cyprus	Access through Individual Reimbursement
Czech Republic	Reimbursed access -Types I, II and IIIa (subject to clinical criteria)
Denmark	Reimbursed access – presymptomatic, Type I & II (subject to clinical criteria)
England & Wales	NICE published in August its Appraisal Consultation Document (ACD), outlining a 'minded no' for the routine funding of nusinersen. The ACD is an interim decision that does not necessarily reflect the final technology guidance. There has been a public consultation period and NICE committee meeting took place on 23 October to review the feedback. Ongoing discussions are underway with all stakeholders
Estonia	Negotiations underway
Finland	Reimbursed access for patients up to, and including, 17 years old, aligned with PALKO positive recommendation
France	Negotiations underway; current reimbursed access given to Types I, II and III through post ATU
Germany	Reimbursed access in line with the label - 5q spinal muscular atrophy (SMA)
Greece	Reimbursed access for pre-symptomatic, Types I and II; negotiations for Type III underway
Hungary	Biogen & NEAK agreement signed. Final access decisions will be made by NEAK as per the Rare Disease Committee criteria in response to all individual applications
Iceland	Reimbursed access – Types I, II, III under 18 years old - November 2018
Ireland	Negotiations underway
Israel	Reimbursed access - Types I, II and III
Italy	Reimbursed access - Types I, II and III
Kuwait	Negotiations underway; current access through a named patient programme
Latvia	Submission of P&R dossier - September 2018; negotiations underway
Lithuania	Access through individual reimbursement
Luxembourg	Reimbursed access in line with the label - 5q spinal muscular atrophy (SMA)
Macedonia	Negotiations underway
Montenegro	Negotiations underway

Netherlands	Regular reimbursement for children up to 9·5 years (subject to clinical criteria); involved parties are currently discussing the possibilities of conditional reimbursement for other SMA patients – August 1st 2018
Northern Ireland	Negotiations underway
Norway	Reimbursed access -Types I, II and IIIa (0 to 18 years of age)
Poland	Reimbursed access in line with the label - 5q spinal muscular atrophy (SMA)
Portugal	Reimbursed access in line with the label - 5q spinal muscular atrophy (SMA)
Qatar	Reimbursed access in line with the label - 5q spinal muscular atrophy (SMA)
Romania	Reimbursed access in line with the label -5q spinal muscular atrophy (SMA)
Russia	Partner in place; Registration dossier was submitted in November 2018
Saudi Arabia	Negotiations underway; current access through a named patient programme
Scotland	Reimbursed Access Type I (later-onset patients funded via the Individual Treatment Fund); negotiations for Type II and III in preparation
Serbia	Access through a named patient programme
Slovakia	Reimbursed access -Types I, II and IIIa - August 1st 2018
Slovenia	Reimbursed access Types I, II and III that are treated in pediatric centers
Spain	Reimbursed access - Types I, II and III
Sweden	Reimbursed access – Pediatric (initiated below 18 years old) Types I, II and IIIa
Switzerland	Reimbursed access (pre-symptomatic and Type I, II, III) up to 20 years old; Individual reimbursement for patients above 20
Turkey	Negotiations ongoing; current access through a named patient programme
Ukraine	Partner in place; preparing for reimbursement dossier submission
UAE	Reimbursed access - in line with the label - 5q spinal muscular atrophy (SMA)

31 January 2019

Single Technology Appraisal (STA)

Nusinersen for treating spinal muscular atrophy [ID1069]

Dear Michael and Jonathan

We would like to set up a teleconference with yourselves, RTI, NICE and the ERG to gain a better understanding of the latest model submitted to NICE. Specifically, in your most recent submission the "Plateauers" sub-models have been reintroduced. This reintroduction increases the complexity in understanding the logic of the model.

We would appreciate if you updated the figure and table used previously by the ERG available in the NICE docs link: https://appraisals.nice.org.uk/request/71781

Additionally could you explain if the proposed MAA nusinersen stopping rules (2 consecutive worsening) remain and if so how this is implemented in the new early and later onset models. If possible could you get this back to us **by 5:00pm on Friday 1 February**, so we have a chance to review the information before the teleconference.

We would have availability on Monday 4 February (pm only, before 4:00pm) to discuss this by teleconference. Could you liaise with Jo to confirm a date and time.

Best Wishes,

Thomas Strong

Health Technology Assessment Adviser

Figure 1: General model structure for company's post-ACD model

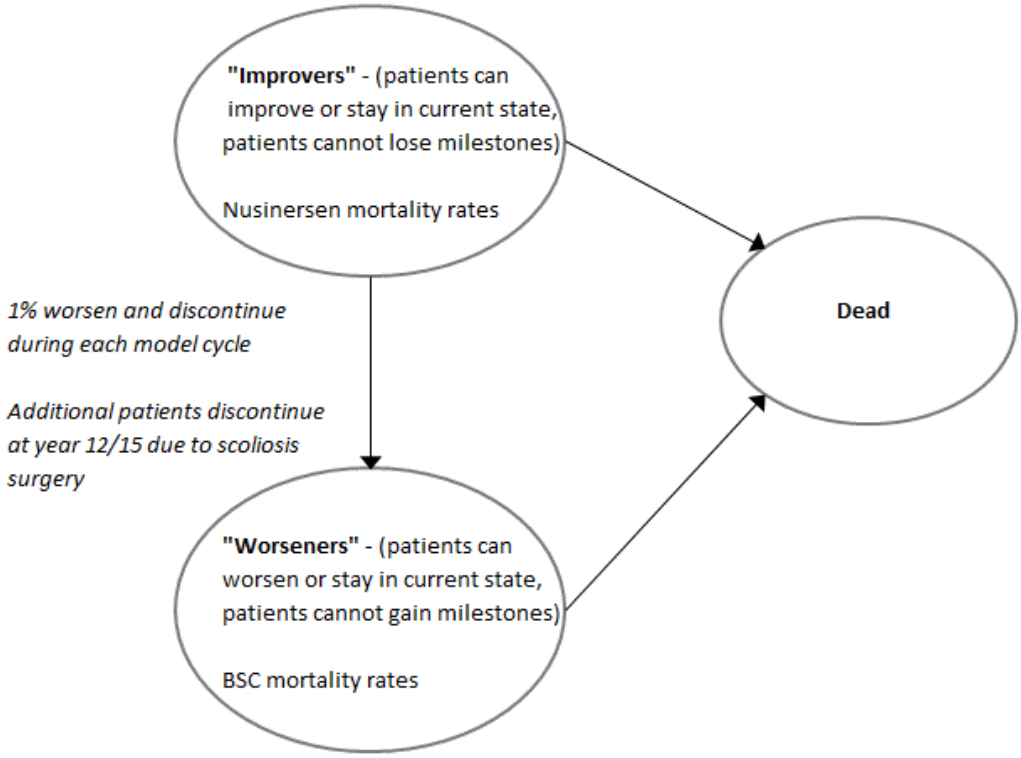


Table 1: Summary of company's sub-model structure for early and later onset models

Sub-model number	Sub-model description	How patients enter this sub-model	Transition matrix and mortality risks applied in sub-model	How patients leave this sub-model
1	No scoliosis surgery, on treatment ("improvers")	All patients except those with no milestones at the end of the observed period are assumed to start in this sub-model at the beginning of the extrapolation period	"Improvers" matrix, nusinersen mortality risk	(a) 1% patients assumed to become "worseners" during each cycle, move to sub-model 3 (b) Scoliosis surgery, on treatment (stay "improver"), move to sub-model 5 (c) Scoliosis surgery, discontinue (become "worsener"), move to sub-model 4 or sub-model 7 (c) Death
2	No scoliosis surgery, on treatment ("plateauers")	Redundant – patients never enter sub-model 2	"Plateauers" matrix i.e. probability=1 on matrix diagonal, nusinersen mortality risk	Redundant – patients never enter sub-model 2
3	No scoliosis surgery, discontinue ("worseners")	1% of all nusinersen "improvers" (each cycle) from sub-model 1	BSC ("worseners") matrix, BSC mortality risk	Death
4	Scoliosis surgery, discontinue	From sub-model 1	BSC ("worseners") matrix, BSC mortality risk	Death
5	Scoliosis surgery, on treatment ("improvers")	A proportion of patients move here from sub-model 1 at the time of scoliosis surgery (dependent on ambulatory status)	"Improvers" matrix, nusinersen mortality risk	(a) 1% patients assumed to become "worseners" during each cycle, move to sub-model 7 (b) death
6	Scoliosis surgery, on treatment ("plateauers")	Redundant – patients never enter sub-model 6	"Plateauers" matrix i.e. probability=1 on matrix diagonal, nusinersen mortality risk	Redundant – patients never enter sub-model 6
7	Scoliosis surgery, discontinue ("worseners")	1% of all post-surgery nusinersen "improvers" (each cycle) from sub-model 1 or sub-model 5	BSC ("worseners") matrix, BSC mortality risk	Death

Figure 1: General model structure for company's post-ACD model – infantile onset

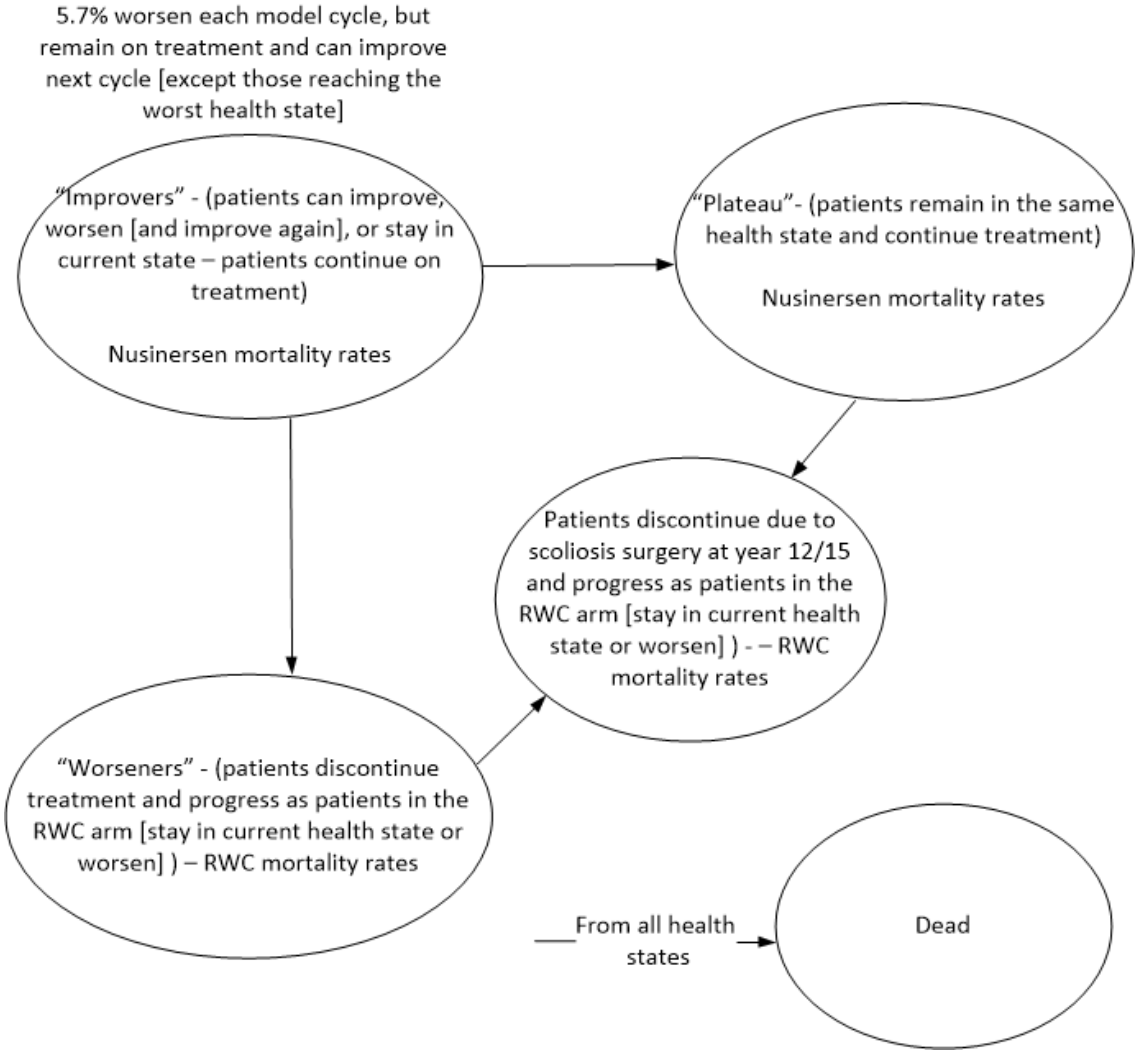


Table 1: Summary of company's sub-model structure for infantile model

Sub-model number	Sub-model description	How patients enter this sub-model	Transition matrix and mortality risks applied in sub-model	How patients leave this sub-model
1	No scoliosis surgery, on treatment ("improvers")	All patients except those with no milestones at the end of the observed period are assumed to start in this sub-model at the beginning of the extrapolation period	"Improvers" matrix, nusinersen mortality risk (5.7% worsen each model cycle, but remain on treatment and can improve at the next cycle [except those reaching the worst health state])	(a) 25% of patients in the mild and moderate health states and 16% of patients in the sits without support health state are assumed to become "worseners" at month 53, move to sub-model 3. 13% of patients in the stands with assistance and the walks with assistance health states are assumed to become "worseners" at month 63, move to sub-model 3. (b) 75% (i.e. 100%-100%*25%) of patients in the mild and moderate health states and 84% of patients in the sits without support health state are assumed to become "plateauers" at month 53, move to sub-model 2. 87% of patients in the stands with assistance and the walks with assistance health states are assumed to become "plateauers" at month 63, move to sub-model 2. (c) After year 12/15 patients with scoliosis surgery, on treatment (stay "improver"), move to sub-model 5 (d) After year 12/15 patients with scoliosis surgery, on treatment (become "plateauers"), move to sub-model 6 (e) patients with scoliosis surgery that discontinue (become "worsener"), move to sub-model 4 or sub-model 7 (f) Death

2	No scoliosis surgery, on treatment (“plateauers”)	At month 53, 75% from health states mild milestones and moderate milestones and 84% from sits without support of all nusinersen “improvers” from sub-model 1 At month 63, 87% from health states stands with assistance and walks with assistance of all nusinersen “improvers” from sub-model 1	"Plateauers" matrix i.e. probability =1 on matrix diagonal, nusinersen mortality risk	(a) After year 12/15 patients with scoliosis surgery, on treatment (“plateauers”) move to sub-model 6 (b) After year 12/15 patients with scoliosis surgery, discontinue treatment (“worseners”) move to sub-model 4 (c) Death
3	No scoliosis surgery, discontinue (“worseners”)	At month 53, 25% from health states mild milestones and moderate milestones and 16% from sits without support of all nusinersen “improvers” from sub-model 1 At month 63, 13% from health states stands with assistance and walks with assistance of all nusinersen “improvers” from sub-model 1	BSC (“worseners”) matrix, BSC mortality risk	Death
4	Scoliosis surgery, discontinue due to scoliosis surgery	Patients on treatment (“improvement” and “plateauers”; from sub-model 1 and sub-model 2, respectively). *Patients from sub-model 1 do not reach this sub-model because there are no “improvers” at the time of scoliosis surgery	BSC (“worseners”) matrix, BSC mortality risk	Death
5	Scoliosis surgery, on treatment (“improvers”)	A proportion of patients move here from sub-model 1 at the time of	“Improvers” matrix, nusinersen mortality risk	(a) patients assumed to become “worseners” in the same way as for

		scoliosis surgery (dependent on ambulatory status) *Patients do not reach this sub-model because there are no “improvers” at the time of scoliosis surgery		“improvers” without scoliosis surgery in sub-model 1, move to sub-model 7 (b) patients assumed to become “plateauers” in the same way as for “improvers” without scoliosis surgery in sub-model 1, move to sub-model 6 (c) death
6	Scoliosis surgery, on treatment (“plateauers”)	Patients “improvers” from sub-model 1, “plateauers” from sub-model 2, “improvers with scoliosis surgery” from sub-model 5	"Plateauers" matrix i.e. probability=1 on matrix diagonal, nusinersen mortality risk	Death
7	Scoliosis surgery, discontinue (“worseners”)	Patients “improvers” that worsen from sub-model 1 and sub-model 5. *Patients do not reach this sub-model because there are no “improvers” at the time of scoliosis surgery	BSC (“worseners”) matrix, BSC mortality risk	Death

Logical test

The "plateauers" submodels were not activated in the previous iteration of the model – patients receiving nusinersen could only be "improvers" or "worseners". Consequently, the ERG needs to verify that this aspect of the model behaves as expected and is not subject to errors. Below describes a logical test to assess this, based on the company's new version of the model.

MODEL A – Transitions and available sub-models based on previous post-ACD iteration

- Disable the possibility of plateauing (all patients are initially improvers)
- Set the probability of moving from the improvers submodel to the worseners submodels equal to 1% in each cycle
- Set the probability of staying in the plateauers submodel equal to zero (patients do not spend any time in plateauing)
- Record QALYs, costs and the ICER for Model A

MODEL B – Model which uses plateau submodels in place of improvers submodels

- Send all improvers immediately to the plateauers submodel
- Set the transition matrix for the plateauers equal to that for the improvers
- Set the probability of worsening equal to the values for the improvers submodel (1% in each cycle)
- Record QALYs, costs and the ICER for Model A

If the plateauers submodels are operating correctly, the results for Model (A) and Model (B) should be identical. We have listed how these two scenarios are implemented in the model below.

List of steps for setting up model A

- Go to efficacy T1 sheet, select "NO" in drop-down box in cell B111 – there is no need to set this to NO. The settings below can be entered in the Efficacy T1 (input sheet).
- In the same sheet, set value in cell I157 equal to "0" (see footnote*)
- Go to "Markov Nusinersen T1" cells BH8:BN8. Set all values equal to "13" - there is no need to set this to 13; can be set to 26.
- In the same worksheet, set values in cell BG9 equal to "1", values in cells BH9:BN9 equal to "0.01" and values in cells BP9:BW9 equal to "1"
- This gives the following results: inc. QALYs = 3.29, inc. costs = [redacted], ICER = [redacted]

List of steps for setting up model B

- Using Model A, go to worksheet "Markov Nusinersen T1" and copy matrix in F471:M478 – paste matrix into cells F495:L502
- In the same worksheet, set values in cells BG9:BN9 equal to "1" and values in cells BQ9:BW9 equal to "0.01"

- This gives the following results: inc. QALYs = 4.77, inc. costs = [redacted], ICER = [redacted]

** When these changes are made, the model gives a "check patient count" error message. This may warrant investigation*

This message can be disregarded as it just checks that at each cycle the sum equals 1000. If the check is 0 then the check returns "ok". The sum is returning 0.0000000004, which is a difference that can be disregarded.

Please explain why the results produced from these two models are not the same

- Aligned with the updated figure provided for additional query 1 (response provided 1st Feb):
  - Once a patient enters the plateau subgroup patients only become worseners due to scoliosis surgery discontinuation. Therefore, the previous check does not apply.
- In model A, after month 26, 1% of improvers become worseners each cycle. However, in model B, after month 26, 99% of patients become plateauers and 1% worseners.

An alternative check could be performed using scoliosis surgery discontinuation as follows (using list price):

- Model A
  - Efficacy T1 worksheet
    - Set scoliosis surgery to 0% (cell F59 in Efficacy T1 sheet)
    - In the same sheet, set value for "% of patients worsening by 1 milestone among patients receiving nusinersen" (cell I157) equal to "0"
    - Set "Month after which a proportion of patients still on treatment stop improving and remain in the same health state" (cells I117:I121) to "26" (i.e. month of last assessment in of SHINE)
    - Set "% patients still on treatment who stop improving" cells I127:I128 to "0" and cells I129:I132 to 1%.
    - Set "% of patients of those reaching an improvement plateau which start getting worse" cells I139:I140 to 0%, and cells I141:I144 equal to 100%.
  - This gives the following results: Inc. QALYs = 3.43, Inc. costs = [redacted] ICER = [redacted]
- Model B
  - Efficacy T1 worksheet
    - Set "% patients that discontinue after scoliosis surgery" (cell I55 to 100%)
    - Set "% patients having scoliosis surgery " (cell F59 to 1%)
    - Set year starting scoliosis to 26/12 (F63, F66)
    - Set I117 to I121 to 26
    - Set I127 and I128 to 0 and I129 to I132 to 100%. In the same worksheet, set values in cell I139 to I144 equal to 0%.
  - Using Model A, go to worksheet "Markov Nusinersen T1" and copy matrix in F471:M478 – paste matrix into cells F495:L502
  - This gives the same results as model A: Inc. QALYs = 3.43, Inc. costs = [redacted] ICER = [redacted]

Additional scenarios Infantile-Onset model

- The current base case assumes that at the defined months (53 and 63), a percentage of patients from each health state become worseners ([redacted]) and the rest plateauers (i.e. there are no improvers).
    - Results: Inc. QALYs = 2.64, Inc. costs = [redacted], ICER = [redacted]
- The upper and lower bounds of a scenario where a percentage of plateauers would worsen each cycle (until all have become worseners) would be given by the following scenarios:
    - A scenario where 0% of patients worsen produces the following results: (Inc. QALYs = 2.88, Inc. costs = [redacted], ICER = [redacted])
    - A scenario where 100% of patients worsen produces the following results: (Inc. QALYs = 1.19, Inc. costs = [redacted], ICER = [redacted])

- A proxy to a scenario where a percentage of plateauers worsen can be set as follows:
    - Set the "improvers" to "plateauers" by setting I154 to 0 and I157 to 0%. This applies the assumption that after trial follow-up patients remain in the same health state (conservative assumption)
        - The month at which patients plateau becomes the month at which a percentage of patients worsen
    - On T1 Efficacy sheet set cells I127:I132 to [redacted] respectively. In the same worksheet, set values in cells I139:I144 equal to 100%.
        - This gives the following results: Inc. QALYs = 0.97, Inc. costs = [redacted] ICER = [redacted]
    - When 100% of patients worsen at the selected months (plateau before that), the results are: Inc. QALYs = 0.79, Inc. costs = [redacted], ICER = [redacted]
    - When 0% of patients worsen and remain in the same health state after the end of trial follow-up, the results are: Inc. QALYs = 1.73, Inc. costs = [redacted], ICER = [redacted]

Additional scenarios Later-Onset model

- The current base case assumes that at the defined months (15/25), a percentage of patients from each health state become worseners ([redacted]) and the rest plateauers (i.e. there are no improvers).
    - Results: Inc. QALYs = 2.56, Inc. costs = [redacted] ICER = [redacted]
- The upper and lower bounds of a scenario were a percentage of plateauers would worsen each cycle (until all have become worseners) would be given by the following scenarios:
    - A scenario where 0% of patients worsen produces the following results: (Inc. QALYs = 2.86, Inc. costs = [redacted], ICER [redacted])
    - A scenario where 100% of patients worsen produces the following results: (Inc. QALYs = 1.15, Inc. costs = [redacted], ICER = [redacted]

- A proxy to a scenario where a percentage of plateauers worsen can be set as follows:
    - On T2 Efficacy sheet set the "improvers" to "plateauers" by setting cell I141 to 0% and cell I144 to 0%. This applies the assumption that after trial follow-up (month 15) patients remain in the same health state (conservative assumption)

        - The month at which patients plateau becomes the month at which a percentage of patients worsen
    - Set cells I108:I112 to [redacted] %. In the same worksheet, set values in cell I119:I123 equal to 100%.
        - This gives the following results: Inc. QALYs = 0.96, Inc. costs = [redacted] ICER = [redacted]
    - When 100% of patient worsen at the selected months (plateau before that), the results are: Inc. QALYs = 0.81, Inc. costs = [redacted] ICER = [redacted]
    - When 0% of patient worsen and remain in the same health state after the end of trial follow-up, the results are: Inc. QALYs = 2.50, Inc. costs = [redacted] ICER = [redacted]

Questions for company 15/02/2019

1. Please confirm that the following is accurate with respect to modelled mortality risk in the early onset population:
    - In the observed period, mortality is modelled using a Weibull model fitted to ENDEAR data (with additional data from SHINE in the nusi group) using a jointly fitted model (using a treatment-indicating covariate i.e. a hazard ratio)
    - In the extrapolated period, mortality in the best states for the nusi group is modelled using a proportionate split of survival rates from Zerres and the tapered HR-adjusted survival rates from the jointly fitted Weibull. Survival in the worst states is modelled using the tapered HR-adjusted Weibull.
    - For the BSC group, the mortality adjustment is also applied in the best states, but the model uses a split of Zerres and the control group Weibull (without the HR). In the worst states, the control group Weibull only is used.

2. In the early onset model, the inclusion of data from SHINE has a substantial impact on the rate of improvement in CHOP INTEND for the nusi group. Why? How has this rate been calculated?

3. Apologies if I've asked this before, but please clarify how the Markov trace in the nusinersen group is being calculated in the observed period. I'm slightly unclear how the death count data are being used together with the mortality risk from the Weibull. A simple mock-up might be helpful and would save me some time unpicking this part of the model.

4. Why was the loss of sitting ability not included in previous versions of the model?

Questions for company 15/02/2019

1. Please confirm that the following is accurate with respect to modelled mortality risk in the early onset population:
    - In the observed period, mortality is modelled using a Weibull model fitted to ENDEAR data (with additional data from SHINE in the nusi group) using a jointly fitted model (using a treatment-indicating covariate i.e. a hazard ratio)
        - The Weibull function was fitted to each arm separately. We did not use a jointly fitted model using a treatment-indicating covariate as the previous models fitted to the ENDEAR data did not show major differences between the unstratified and the stratified models (Figure 1) and because the integrated brier score showed that unstratified models gave a poor reliability (with the exception of the Gompertz model; Figure 2).
        - The selected parametric functions for the RWC arm were selected based on plausibility of long-term prediction. We included only those functions that predicted less than 20% of survivors at 10 years (natural history data showed estimates at 10 years between 0% and 10% [Zerres and Rudnik-Schoneborn 1995; Farrar et al., 2013; Ge et al., 2012]). Survival estimates greater than 20% under standard of care by 10 years were considered as unlikely by clinical experts

Figure 1: Standard Parametric Models Fitted to the ENDEAR Trial Data: Overall Survival

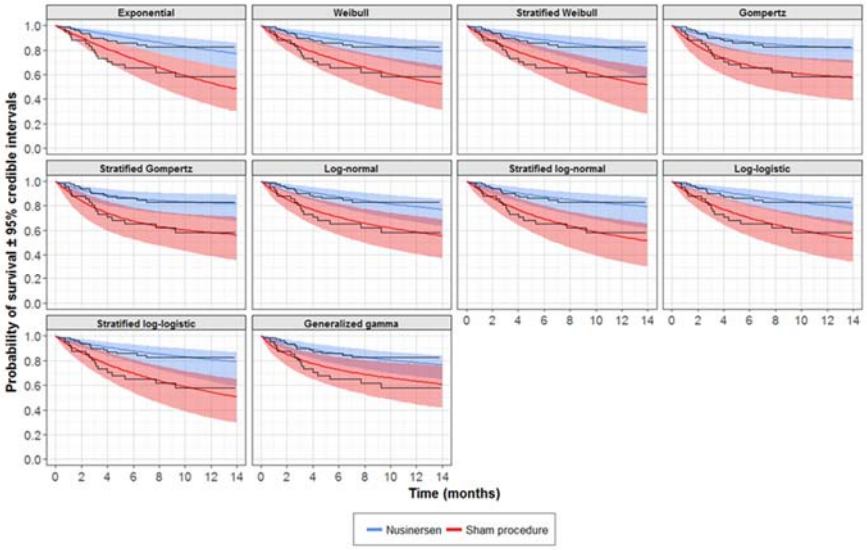
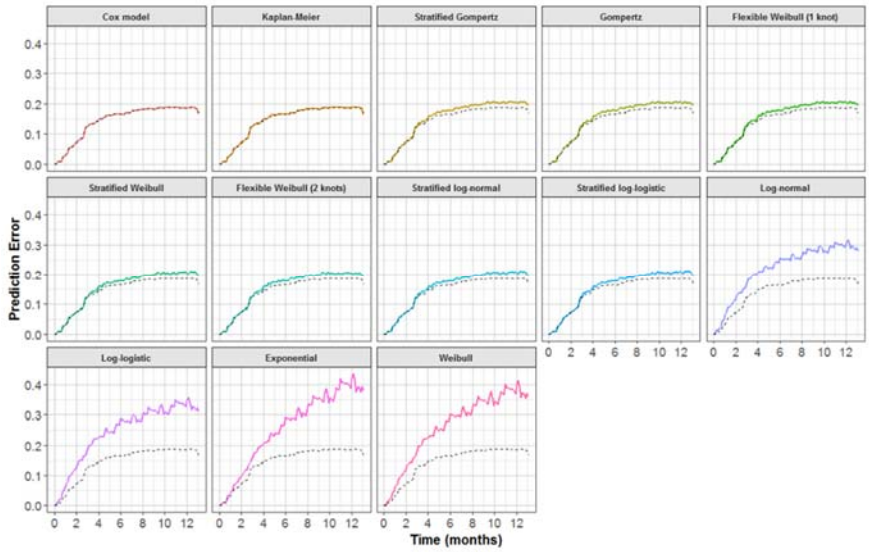


Figure 2: Prediction Error Curves Derived From Bootstrap Cross-Validation for the Models Fitted to Overall Survival From the ENDEAR Trial Data



Note: Dotted line represents model with lowest integrated Brier score.

- The following scenario was run in the latest model using the parameters of the stratified and unstratified Weibull functions fitted to the ENDEAR data. The stratified models resulted in a lower survival difference, with a negligible impact on the ICER.

Stratified Weibull	Nusinersen	RWC
Scale	102.156	22.79
Shape	0.73	0.81

Unstratified Weibull	Nusinersen	RWC
Scale	88.952	23.90
Shape	0.77	0.77

	Mean OS – Nusinersen	Mean OS - RWC	OS difference	ICER (list price)
Stratified Weibull	7.89	2.14	5.75	429,465
Unstratified Weibull	8.35	2.32	6.02	429,258

- In the extrapolated period, mortality in the best states for the nusi group is modelled using a proportionate split of survival rates from Zerres and the tapered HR-adjusted survival rates from the jointly fitted Weibull. Survival in the worst states is modelled using the tapered HR-adjusted Weibull.
  - Correct (note that the Weibull function was fitted to each arm separately)

- For the BSC group, the mortality adjustment is also applied in the best states, but the model uses a split of Zerres and the control group Weibull (without the HR). In the worst states, the control group Weibull only is used.
    - Correct (note that the Weibull function was fitted to each arm separately)

2. In the early onset model, the inclusion of data from SHINE has a substantial impact on the rate of improvement in CHOP INTEND for the nusi group. Why? How has this rate been calculated?
    - The mean rate of CHOP INTEND from day 394 to day 818 was calculated as the average of the individual change in score from day 394 for the 11 patients that had a day 818 assessment divided by the number of weeks between the assessment points: mean change from day 394 to day 818 / weeks = 5.36/61 = 0.088/week = 0.38/month.
    - As more patients reach the 818 assessment, it is likely that the rate of CHOP INTEND change will increase as many of the patients with the highest score change up to day 394 (N=47) did not have a day 818 assessment (N=11).

3. Apologies if I've asked this before, but please clarify how the Markov trace in the nusinersen group is being calculated in the observed period. I'm slightly unclear how the death count data are being used together with the mortality risk from the Weibull. A simple mock-up might be helpful and would save me some time unpicking this part of the model.
    - The model calculates the difference between the percentage of patients alive estimated from the observed count and the survival estimated from the Weibull function. Then the difference in survival is distributed in all the health states weighted by the percentage of patients in each health state. For example:
    - At month 6, the Weibull function estimates a survival of 89.07% while the survival estimated from the observed count is 86.52% (transition matrix for month 6; F362:N370). With a starting cohort of 1000, this difference is equivalent to 25.44 patients.
    - Under each transition matrix in the Markov Nusinersen T1 sheet, we estimate the health state membership without the survival adjustment. For month 6, in F373:M373 we estimate the health state membership based on the previous cycle and the transition matrix for month 6. In F374:M374, we estimate the percentage of patients in each health state.

No Miles.	Mild. Miles.	Mod Miles.	Sits w	Stands w	Walks w	S/W w/o	Loss
183.2	297.0	316.5	68.5	0.0	0.0	0.0	0.0
21%	34%	37%	8%	0%	0%	0%	0%

    - We use the weights to distribute the 25.44 in all health states.

	No Miles.	Mild. Miles.	Mod Miles.	Sits w	Stands w	Walks w	S/W w/o	Loss
	183.2	297.0	316.5	68.5	0.0	0.0	0.0	0.0
	21%	34%	37%	8%	0%	0%	0%	0%
25.45	5.389	8.736	9.307	2.015	0.000	0.000	0.000	0.000
Month 6	188.63	305.76	325.76	70.54	0.00	0.00	0.00	0.00

4. Why was the loss of sitting ability not included in previous versions of the model?
    - There were no observations of loss of sitting in later onset SMA in either sham or nusinersen in CHERISH, this is most likely due to the ae of the cohort in addition to the trial duration being cut short (15 months)
    - In clinical validation of the original global model structure, the exclusion of this health state was not raised as a limitation. Only in clinical validation conducted prior to this latest submission was this issue raised by experts. As agreed with the NICE technical team in January, it was determined not to introduce a new health state at this stage in the process based on this feedback.

Nusinersen for treating spinal muscular atrophy: A Single Technology Appraisal

Addendum 2: ERG comments on company's revised models and additional economic analyses

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1. Introduction

In August 2018, NICE issued its ACD[1] which made the following recommendation: *"Nusinersen is not recommended, within its marketing authorisation, for treating 5q spinal muscular atrophy."* (NICE ACD,[1] 2018).

In response to the NICE ACD,[1] the company submitted the following to NICE: (i) an overall ACD response document;[2] (ii) a supplementary appendix[3] reporting additional data from the ENDEAR and SHINE studies;[4, 5] (iii) a supplementary appendix detailing modifications to the company's original early and later onset SMA models, including a new commercial access agreement,[6] and (iv) revised executable models for the early onset and later onset SMA populations. In response to these documents, the ERG produced a critique of the company's new evidence and analyses.[7] This evidence was discussed at the second NICE Appraisal Committee meeting in October 2018. NICE did not issue a revised ACD following this meeting.

In December 2018, the company, the ERG and NICE attended a meeting to discuss the Appraisal Committee's concerns regarding the company's previous economic analyses and to explore how these might be addressed using the company's models. In January 2019, the company submitted further revised versions of their early and later onset SMA models together with an addendum[8] which outlines additional evidence and alternative assumptions applied within these analyses. [redacted]

This ERG addendum provides a summary and critique of the company's new analyses. The addendum refers to the following three pairs of health economic models submitted to NICE by the company:

- The "original models" – the early and later onset SMA models submitted by the company as part of their original submission to NICE[9] (March 2018)
- The "post-ACD models" – the early and later onset SMA models submitted as part of the company's response to the NICE ACD[6] (September 2018)
- The "current models" – the early and later onset SMA models submitted following the second NICE Appraisal Committee meeting[8] (January 2019).

The document is set out as follows. Section 2 summarises the amendments applied within the company's current early and later onset models, the logic and implementation their revised structures and the results generated by the company using these amended models. Section 3 presents the results

of the ERG's model verification exercise and presents a commentary on the amendments applied within the company's current early and later onset models. Section 4 presents additional analyses of the company's current models undertaken by the ERG. Section 5 draws conclusions based on the analyses undertaken by the company and the ERG.

Four additional appendices are presented for information:

- Appendix 1 presents condensed versions of the Markov traces and overall survival projections for the company's current early and later onset models
- Appendix 2 summarises the HRQoL and cost estimates applied in each iteration of the company's early and later onset models
- Appendix 3 presents a breakdown of the results generated using the company's original models, the post-ACD models and the current models
- Appendix 4 shows the impact of applying the company's current PAS within the company's original models, the post-ACD models and the current models.

2.1 Early onset model - summary of model structure, parameters and results

2.1.1 Amendments made to the company's early onset model

Box 1 summarises the amendments that have been made within the current version of the company's early onset model (relative to the post-ACD version).

Box 1: Amendments applied in the company's current early onset model (relative to the company's post-ACD model)

- Model structure
  - Structural amendment which applies a plateau for a proportion of "improvers" in each health state at age 5 or 6 years (state-dependent); the remainder are assumed to become "worseners." No patient aged >6 years is assumed to be an improver.
- Transition probabilities
  - Transition probabilities for nusinersen group during the observed period updated to include data from SHINE[5] (observed period increased from 13 months to 26 months)
  - Transition probabilities for "improvers" during the extrapolation period amended to include the possibility of temporary or continued worsening (whilst remaining an "improver" on treatment, based on SHINE).
  - Rate of improvement in CHOP INTEND score for "improvers" based on ENDEAR[4] and SHINE (day 394-818).
- Mortality
  - Weibull survival model updated to include data from ENDEAR and SHINE in nusinersen group.
  - Tapering of hazard ratio (HR) for nusinersen versus BSC increased from 60 months to 120 months.
  - State-dependent mortality adjustment factor applied for health states consistent with Type 2/3 SMA (states [iv] to [vii] – from sits without support to walks unaided).
- Resource use and costs
  - Health state costs from company's RWE survey[9] updated to reflect values from Great Ormond Street Hospital (GOSH) and Newcastle Trust only (data from other centres excluded).
  - Type I SMA costs from real-world evidence (RWE) survey doubled.
- Health-related quality of life
  - Patient utility values based on company's experts' HRQoL values.[8]
  - Number of caregivers increased to 3.
- Commercial offer

[redacted]

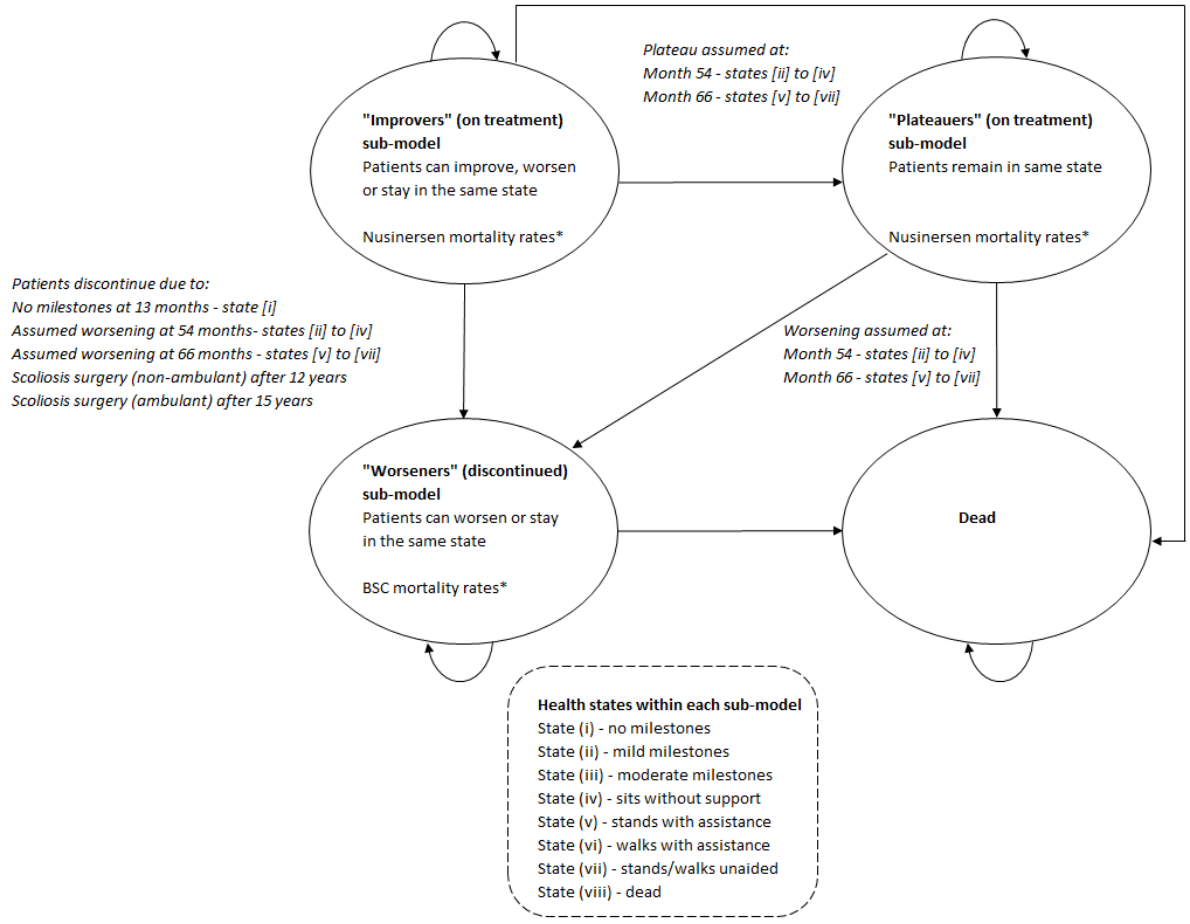
2.1.2 Description of company's current model structure and logic – early onset population

This section provides a description of the company's current early onset model; a critique of the model can be found in Section 3 of this addendum.

The company's current early onset model is based on the sub-model approach used in the company's post-ACD early onset model.[1] Broadly speaking, the sub-models characterise the impact of the disease and treatment using nusinersen across three groups of patients: (i) "improvers (on treatment)" – patients

who are receiving nusinersen treatment and are following a general trajectory of improvement; (ii) "plateauers (on treatment)" – patients who are still receiving nusinersen treatment but have reached a plateau in benefit, and; (iii) "worseners (discontinued)" – patients who are no longer receiving, or have never received, nusinersen treatment, and are following a trajectory of worsening. Whilst the company's implemented model includes four additional sub-models which account for patient outcomes following scoliosis surgery, these sub-models have the same general characteristics as the pre-scoliosis surgery sub-models (after surgery, patients are classed as improvers, plateauers or worseners), hence they do not require further explanation in order to understand the overall logic of the model structure. The sub-models are assumed to be associated with different permitted transitions and different survival prognoses, depending on time elapsed since model entry and whether the patient is receiving treatment with nusinersen. The company's overall sub-model structure for the early onset population is summarised in Figure 1 and the subsequent text.

Figure 1: Company's current early onset SMA sub-model structure (drawn by the ERG)



Note: Each ellipse shows the permitted health state transitions within each sub-model. At the point at which the plateau is assumed to occur (age 5 or 6 years, depending on health state), all patients in those states become plateauers or worseners and none remain improvers.
** Mortality adjustment factor applied to better health states. Improved survival associated with worst states in nusinersen group applied up to month 146.*

Patients enter the early onset model according to the distribution of patients in ENDEAR[4] at baseline. During the observed period, patients transition between the model health states (defined by motor milestones) according to patient count data from ENDEAR (up to month 13) for the BSC group and according to patient count data from ENDEAR plus SHINE[5] (up to month 26) for the nusinersen group. Mortality risk is modelled using a Weibull function fitted to time-to-event data from ENDEAR only for BSC and ENDEAR plus SHINE for nusinersen; separate survival models were fitted to each treatment group during this period.

During the extrapolation period, patients in the nusinersen group are defined as "improvers (on treatment)", "plateauers (on treatment)" or "worseners (discontinued)." During each model cycle, improvers can transition to the next best health state, remain in their current health state or transition to the next worst health state. Plateauers can only remain in their current health state. Worseners can transition to the next worst health state or remain in their current health state. Improvers and plateauers are assumed to have an improved survival prognosis in all states relative to BSC up to 120 months after the end of the observed period of ENDEAR and SHINE (based on the Weibull model, adjusted using an HR of 0.37 from the ENDEAR trial, tapered to 1.0 by month 146). Within each sub-model, patients in the better health states (those which are consistent with Type 2/3 SMA - states [iv] to [vii]) are assumed to have a further improved survival prognosis relative to patients in the worst health states (states [i] to [iii]); this improved survival prognosis is implemented using a mortality adjustment factor which apportions 75% of the mortality risk from the model based on data reported by Zerres *et al*[10] and 25% of the mortality risk from the tapered HR-adjusted Weibull model fitted to the data from ENDEAR and SHINE[5] to patients in these better states. This mortality adjustment factor applies to the nusinersen group, but not the BSC group. Worseners are assumed to have a poorer survival prognosis based on the Weibull function for the BSC group. Patients mix across the sub-models at five discrete timepoints:

- At month 26, patients in state [i] (no milestones) are assumed to become worseners (although these patients are also assumed to have discontinued treatment with nusinersen earlier at month 13); the remainder are initially assumed to be improvers. Patients in the other health states remain as improvers.
- At month 54, [redacted] of improvers in state [ii] (mild milestones) and state [iii] (moderate milestones) and [redacted] of patients in state [iv] (sits without support) are assumed to become worseners; the remainder are assumed to become plateauers. These proportions are based on a weighted average of the proportion of patients worsening at each assessment in the CHERISH later onset trial.[11] Patients in the other states who were improvers remain as improvers.
- At month 66, [redacted] of improvers in state [v] (stands with assistance) to state [vii] (walks unaided) are assumed to become worseners; the remainder are assumed to become plateauers. These proportions are also based on CHERISH.[11] After this timepoint, no patient in any state remains an improver – all are assumed to be either plateauers or worseners.

- After 12 years, 8.6% of non-ambulant plateauers (states [ii] to [v]) are assumed to discontinue nusinersen treatment following scoliosis surgery and subsequently become worseners.
- After 15 years, 8.6% of ambulant plateauers (states [vi] and [vii]) are assumed to discontinue nusinersen treatment following scoliosis surgery and subsequently become worseners.

During the extrapolation period, all patients in the BSC group are assumed to be worseners and cannot achieve additional motor milestones.

The key structural differences between the company's current model[8] and the post-ACD model[6] are: (a) between month 27 and month 66, nusinersen-treated improvers can lose motor milestones (whilst remaining on treatment); (b) after month 66, all nusinersen-treated improvers are subsequently assumed to plateau and cannot gain additional motor milestones, and (c) with the exception of those who discontinue due to scoliosis surgery, patients can only subsequently become worseners at the timepoint at which the plateau is assumed to occur.

Table 1 summarises the main aspects of the company's current model,[8] the post-ACD model[6] and the original model[9] for the early onset SMA population. As shown in the table, all key aspects of the early onset model have changed considerably since the beginning of the appraisal.

Table 1: Main aspects of the company's early onset model – original model, post-ACD model and current model

Model element	Original model[9]	Post-ACD model[6]	Current model[8]
Structure	Single homogenous population represented by time-dependent transition matrices, except for separate matrix applied to patients discontinuing nusinersen treatment following post-scoliosis surgery. Nusinersen-treated patients cannot lose milestones; BSC patients cannot gain milestones.	Modelled using 7 sub-models of patients who are "improvers", "plateauers" or "worseners" with additional separate sub-models for those discontinuing nusinersen treatment post-scoliosis surgery. Plateauer sub-models redundant. Nusinersen-treated patients cannot lose milestones, except for arbitrary 1% of improvers who worsen and discontinue each cycle; BSC patients cannot gain milestones	Modelled using 7 sub-models of patients who are "improvers", "plateauers" or "worseners" with additional separate sub-models for those discontinuing nusinersen treatment post-scoliosis surgery. Plateauer sub-models are activated at fixed timepoints (after months 54 and 66, depending on state). Nusinersen-treated patients can improve, plateau or worsen at various timepoints (see Figure 1); BSC patients cannot gain milestones.
Survival	Piecewise function using ENDEAR[4] and external data.[10, 12, 13] Mortality adjustment factor of 0.90 applied to nusinersen group in states consistent with Type 2/3 SMA (states [iv] to [vii]). The application of this adjustment factor means that patients in these states are apportioned 90% of the improved survival probability and 10% of the worse survival probability.	BSC group – Weibull model fitted to data from ENDEAR.[4] Nusinersen group – Weibull model fitted to ENDEAR data. HR from trial applied and tapered over 60 months. No difference in mortality risk between better and worse health states.	Separate Weibull models fitted to data from ENDEAR[4] (both groups) and SHINE[5] (nusinersen group only). HR from trial applied and tapered over 120 months after end of observed period. Mortality adjustment factor of 0.75 applied to nusinersen group in states consistent with Type 2/3 SMA (states [iv] to [vii]). The application of this adjustment factor means that patients in these states are attributed 75% of the improved survival probability and 25% of the worse survival probability.
Transition probabilities (observed period)	Both groups - patient count data from ENDEAR,[4] days 1-394	Same as original model	BSC group - patient count data from ENDEAR,[4] days 1-394 Nusinersen group - patient count data from ENDEAR,[4] days 1-394 with additional data from SHINE[5] out to day 818

Model element	Original model[9]	Post-ACD model[6]	Current model[8]
Transition probabilities (extrapolation period)	Each group uses arm-specific CHOP INTEND thresholds from ENDEAR[4] and Study CS3A[14] Nusinersen group - mean rate of improvement from ENDEAR ([redacted] points per month) BSC group - mean rate of worsening from ENDEAR ([redacted] points per month)	Both groups use same CHOP INTEND thresholds from ENDEAR[4] and Study CS3A[14] Improvers - mean rate of improvement from ENDEAR ([redacted] points per month) Worseners (and BSC group) - mean rate of worsening from ENDEAR ([redacted] points per month)	Both groups use same CHOP INTEND thresholds from ENDEAR[4] and Study CS3A[14] Improvers – mean rate of improvement from ENDEAR and SHINE[5] (day 394 to 818) ([redacted] points per month). Additional probability of worsening by one health state whilst remaining an improver based on weighted average across timepoints from SHINE ([redacted]). Plateauers – no transitions allowed between states. Proportion of patients becoming worseners (those who do not plateau) based on CHERISH[11] later onset trial. Plateau assumed to occur at 5 or 6 years of age depending on health state, based on clinical opinion received by the company. Worseners (and BSC group) - mean rate of worsening from ENDEAR ([redacted] points per month)
Scoliosis surgery	Non-ambulant patients – 1% at 12 years* Ambulant patients – 1% at 15 years 20% patients discontinue nusinersen after surgery	Non-ambulant patients – 43% at 12 years* Ambulant patients – 43% at 15 years 20% patients discontinue nusinersen after surgery	Same as post-ACD model
Modelled nusinersen stopping rule(s)	Patients discontinue if: (a) no milestones are achieved by end of month 13, or (b) patient cannot receive nusinersen treatment following scoliosis surgery	Patients discontinue if: (a) no milestones are achieved by end of month 13, (b) patient cannot receive nusinersen treatment following scoliosis surgery, or (c) patient becomes a worsener	Patients discontinue if: (a) no milestones are achieved by end of month 13, (b) patient cannot receive nusinersen treatment following scoliosis surgery, or (c) patient becomes a worsener (note - patients can in principle repeatedly worsen whilst still being classed as an improver)

Model element	Original model[9]	Post-ACD model[6]	Current model[8]
Health state costs	Based on milestones associated with SMA types from Bastida *et al*[15]	Based on milestones associated with SMA types from Biogen RWE survey[6]	Based on milestones associated with SMA types from Biogen RWE survey (weighted average of estimates from GOSH and Newcastle Trust only). Type I SMA cost doubled.
Patient utilities	PedsQL data from CHERISH mapped to EQ-5D[9]	EQ-5D vignette study (Lloyd *et al*[16]*)*	Company's experts' HRQoL estimates[8] (not preference-based)
Caregiver utilities	Based on Bastida *et al*[15] plus multiple assumptions linking caregiver utility to patient utility 1 caregiver assumed	"Wide range" utilities based on range defined by mean utility from Spanish caregivers in Bastida *et al*[15] (worst state) and general population utility (best state) 2 caregivers assumed	"Wide range" utilities based on range defined by mean utility from Spanish caregivers in Bastida *et al*[15] (worst state) and general population utility (best state) 3 caregivers assumed.
PAS / access proposal	Simple price discount ([redacted] reduction from list price) proposed prior to first Appraisal Committee meeting.	Complex agreement combined with price discount ([redacted] reduction from list price).	[redacted]

** Scoliosis surgery for non-ambulant BSC patients assumed to occur at 10 years, although this has no impact on estimated health outcomes or costs for this treatment group*

2.1.3 Company's current model results – early onset population

Table 2 presents the results of the company's current base case analysis and additional sensitivity analyses for the early onset population (including the current PAS). It should be noted that the results tables in the company's addendum contain some labelling errors; Table 2 includes the correction of these errors. Based on the deterministic version of the company's current model, the base case ICER including only patient health gains is estimated to be [redacted] per QALY gained. The lowest ICER generated from the company's sensitivity analyses (including patient health gains) is [redacted] per QALY gained (company's analysis S3 – mortality adjustment factor increased to 1.0). When caregiver health losses are also included in the analysis, the deterministic base case ICER is estimated to be [redacted] per QALY gained. The lowest ICER generated from the company's sensitivity analyses (including patient and caregiver QALY losses) is [redacted] per QALY gained (company's analysis S12 - number of caregivers = 1).

With respect to the company's results for the early onset population, the ERG makes the following observations:

- The company's addendum[8] includes a useful range of sensitivity analyses which test the importance of many of the key uncertainties in the model.
- The analyses which include only patient health gains consistently produced ICERs which are greater than [redacted] per QALY gained. This finding is driven by the extension of life for nusinersen-treated patients combined with: (a) the assumption of a plateau in clinical benefit which limits the expected QALY gains, and (b) ongoing drug and disease management costs which together lead to substantial lifetime costs for patients who, based on the model assumptions, would have otherwise died without nusinersen treatment.
- Removing the assumption of an improvement plateau at specific timepoints, lowering the drug costs and assuming lower health state costs, each individually reduce the ICERs for nusinersen versus BSC.
- The inclusion of caregiver QALYs in the analysis disadvantages nusinersen in the early onset SMA population as these health losses are estimated to be greater for carers of nusinersen-treated patients compared with BSC-treated patients. This is a consequence of an increased survival duration for nusinersen-treated patients and imperfect HRQoL for their caregivers. The inclusion of multiple caregivers for each SMA patient increases the magnitude of the incremental caregiver QALY losses for the nusinersen group versus the BSC group.
- As discussed within the company's addendum, applying a zero price for nusinersen within the company's current early onset model leads to ICERs of [redacted] per QALY gained (patient health gains) and [redacted] per QALY gained (patient health gains and caregiver health losses).

A commentary on the company's current early onset model is presented in Section 3 of this addendum.

Table 2: Company's current model results – early onset population (adapted from company's addendum,[8] with corrections)

Option	QALYs (patient)	QALYs (caregivers)	Cost	Inc. QALYs (patient)	Inc. QALYs (caregivers)	Inc. cost	ICER (patient)	ICER (patient+ caregivers)
Revised base case								
Nusinersen	2.64	-4.48	[redacted]	2.64	-1.88	[redacted]	[redacted]	[redacted]
BSC	0.00	-2.61	[redacted]	-	-	-	-	-
S1 – Slower BSC arm decline in CHOP-INTEND (Finkel *et al*[17])								
Nusinersen	2.86	-4.45	[redacted]	2.84	-1.88	[redacted]	[redacted]	[redacted]
BSC	0.02	-2.58	[redacted]	-	-	-	-	-
S2 – Mortality adjustment factor for better health states = 0.5*								
Nusinersen	1.99	-4.02	[redacted]	1.99	-1.42	[redacted]	[redacted]	[redacted]
BSC	0.00	-2.61	[redacted]	-	-	-	-	-
S3 – Mortality adjustment factor for better health states = 1.0*								
Nusinersen	4.37	-5.61	[redacted]	4.37	-3.00	[redacted]	[redacted]	[redacted]
BSC	0.00	-2.61	[redacted]	-	-	-	-	-
S4 – Improvement plateau applied 1 year later								
Nusinersen	2.85	-4.35	[redacted]	2.85	-1.74	[redacted]	[redacted]	[redacted]
BSC	0.00	-2.61	[redacted]	-	-	-	-	-
S5 – Proportion of improvers who can worsen and subsequently improve doubled ([redacted])								
Nusinersen	2.22	-4.61	[redacted]	2.22	-2.00	[redacted]	[redacted]	[redacted]
BSC	0.00	-2.61	[redacted]	-	-	-	-	-
S6 – Proportion of improvers who can worsen and subsequently improve halved ([redacted])								
Nusinersen	2.88	-4.39	[redacted]	2.88	-1.78	[redacted]	[redacted]	[redacted]
BSC	0.00	-2.61	[redacted]	-	-	-	-	-
S7 – Proportion of patients who discontinue per cycle based on last observed assessment*†								
Nusinersen	2.41	-4.48	[redacted]	2.40	-1.87	[redacted]	[redacted]	[redacted]
BSC	0.00	-2.61	[redacted]	-	-	-	-	-
S8 – Proportion of patients who worsen and discontinue at age 5/6 years doubled*								
Nusinersen	2.41	-4.48	[redacted]	2.40	-1.87	[redacted]	[redacted]	[redacted]
BSC	0.00	-2.61	[redacted]	-	-	-	-	-
S9 – Health state costs adjustment factor for Type I SMA equal to 1.5								
Nusinersen	2.64	-4.48	[redacted]	2.64	-1.88	[redacted]	[redacted]	[redacted]
BSC	0.00	-2.61	[redacted]	-	-	-	-	-

Option	QALYs (patient)	QALYs (caregivers)	Cost	Inc. QALYs (patient)	Inc. QALYs (caregivers)	Inc. cost	ICER (patient)	ICER (patient+ caregivers)
S10 – ERG clinical advisors' patient HRQoL estimates								
Nusinersen	3.41	-4.48	[redacted]	2.99	-1.88	[redacted]	[redacted]	[redacted]
BSC	0.42	-2.61	[redacted]	-	-	-	-	-
S11 – 'Narrow range' caregiver utilities (UK subgroup from Bastida *et al*[15])								
Nusinersen	2.64	-3.34	[redacted]	2.64	-1.56	[redacted]	[redacted]	[redacted]
BSC	0.00	-1.77	[redacted]	-	-	-	-	-
S12 – Number of caregivers = 1								
Nusinersen	2.64	-1.49	[redacted]	2.64	-0.63	[redacted]	[redacted]	[redacted]
BSC	0.00	-0.87	[redacted]	-	-	-	-	-

** The results presented in the company's addendum for these scenarios are incorrect due to labelling errors. Corrected values are presented in Table 2.*
† The ERG was unable to implement this sensitivity analysis using the company's model

2.2 Later onset model - summary of model structure, parameters and results

2.2.1 Amendments made to the company's later onset model

Box 2 summarises the amendments that have been made within the current version of the company's later onset model (relative to the post-ACD version).

Box 2: Amendments applied in the company's current later onset model (relative to the company's post-ACD model)

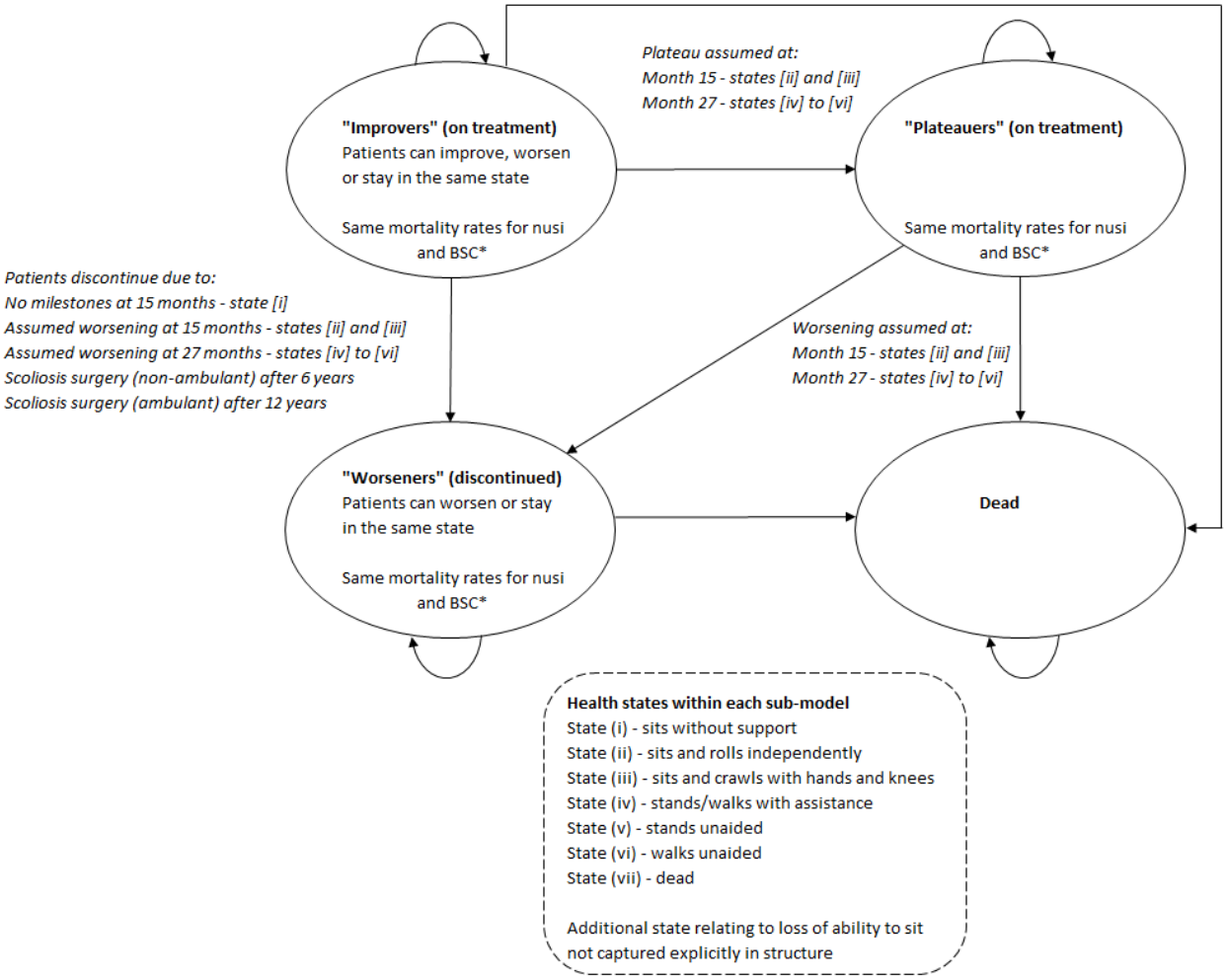
- *Model structure*
  - Structural amendment which applies a plateau for a proportion of "improvers" in each health state at age 5 or 6 years (state-dependent); the remainder are assumed to become "worseners." No patient aged >6 years is assumed to be an improver.
  - Inclusion of additional patient and caregiver QALY losses and Type I SMA costs for patients who lose the ability to sit without support.
- Transition probabilities
  - Transition probabilities for "improvers" during the extrapolation period updated to include the possibility of temporary or continued worsening (whilst remaining an "improver" on treatment, based on CHERISH[11]).
- Mortality
  - State-dependent mortality adjustment factor applied for health states consistent with Type 3 SMA (states [v] and [vi] – stands unaided and walks unaided).
- Resource use and costs
  - Health state costs from company's RWE survey[9] updated to reflect values from GOSH and Newcastle Trust only.
  - Type I SMA costs from RWE survey doubled (applied to patients who lose the ability to sit).
- Health-related quality of life
  - Patient utility values based on company's experts' HRQoL values[8]
  - HRQoL associated with losing ability to sit included based on estimate for early onset model state [iii] (moderate milestones).
  - Caregiver utility values for patients in states [i] to [iii] (sits without support, sits and rolls, and sits and crawls on hands and knees) amended to reflect caregiver utilities applied in early onset model
  - Number of caregivers increased to 3 for patients losing ability to sit.
- Scoliosis surgery
  - Proportion of patients undergoing scoliosis surgery increased to 60%.
  - Timing of scoliosis surgery brought forward for non-ambulant and ambulant patients (after 6 years and 12 years, respectively)
- Commercial offer

2.2.2 Description of company's current model structure and logic – later onset SMA

This section provides a description of the company's current later onset model; a critique of the model can be found in Section 3 of this addendum.

The company's current later onset model is based on the same sub-model approach as the early onset model (previously described in Section 2.1.2), but features some differences with respect to the time at which patients mix across the sub-models. The company's overall sub-model structure for the later onset population is summarised in Figure 2 and the subsequent text.

Figure 2: Company's new sub-model structure – later onset population (drawn by the ERG)



Note: Each ellipse shows the permitted health state transitions within each sub-model. At the point at which the plateau is assumed to occur (age 5 or 6 years, depending on health state), all patients in those states become plateauers or worseners and none remain improvers.
** Mortality adjustment factor applied to better health states. Same survival assumed for patients receiving nusinersen and those receiving BSC in the worst states.*

Patients enter the later onset model according to the distribution of patients in CHERISH[11] at baseline. During the observed period, patients transition between the model health states (defined by motor

milestones) according to patient count data from CHERISH (up to month 15) for both groups. Mortality risk over this period is assumed to be zero, as no deaths occurred in either arm of the trial.

During the extrapolation period, patients in the nusinersen group are defined as "improvers (on treatment)", "plateauers (on treatment)" or "worseners (discontinued)." During any model cycle, improvers can transition to the next best health state, remain in their current health state or transition to the next worst health state. Plateauers can only remain in their current health state. Worseners can transition to the next worst health state or remain in their current health state. Mortality risk in both treatment groups is based on a 2-knot spline model fitted to data reported by Zerres *et al*.[10] Within each sub-model, patients in the better health states (those which are consistent with Type 3 SMA - states [v] and [vi]) are assumed to have an improved survival prognosis relative to the worst health states (states [i] to [iv]); this improved survival prognosis is implemented using a mortality adjustment factor which apportions 75% of the mortality risk from the general population[13] and 25% of the mortality risk from the spline model to patients in these better states. Patients mix across the sub-models at four discrete timepoints:

- At month 15, patients in state [i] (sits without support but does not roll) are assumed to discontinue treatment with nusinersen. [redacted] of patients in state [ii] (sits and rolls independently) and [redacted] of patients in state [iii] (sits and crawls with hands and knees) are also assumed to become worseners at this timepoint; the remainder are initially assumed to be plateauers. These proportions are based on a weighted average of the proportion of patients worsening at each assessment in the CHERISH later onset trial.[11] Patients in the other states are initially classed improvers.
- At month 27, [redacted] of patients in state [iv] (stands/walks with assistance) to state [vi] (walks unaided) are assumed to become worseners; the remainder are assumed to become plateauers. These proportions are also based on the CHERISH later onset trial.[11] After this timepoint, no patient in any state remains an improver – all are assumed to be either plateauers or worseners.
- After 6 years, 12% of non-ambulant plateauers (states [i] to [iii]) are assumed to discontinue nusinersen treatment following scoliosis surgery and subsequently become worseners.
- After 12 years, 12% of ambulant plateauers (states [iv] to [vi]) are assumed to discontinue nusinersen treatment following scoliosis surgery and subsequently become worseners.

During the extrapolation period, all patients in the BSC group are assumed to be worseners and cannot achieve additional motor milestones.

The company's current later onset model includes an additional assumption that all patients who are in state [i] (sits without support but does not roll) will eventually lose their ability to sit (by age 19.5 years,

based on Wadman *et al*.[18]). This is not included as a separate health state, but is instead modelled by applying lower patient utilities, lower caregiver utilities and higher costs (those associated with Type 1 SMA) to the proportion of surviving patients who have lost this milestone.

The key structural differences between the company's current model and the post-ACD model are: (a) between months 15 and month 27, nusinersen-treated "improvers" can lose motor milestones (whilst remaining on treatment); (b) after month 27, no patient receiving nusinersen is assumed to gain additional motor milestones; (c) with the exception of those who discontinue due to scoliosis surgery, patients can only subsequently become worseners at the timepoints at which the plateau is assumed to occur, and (d) the inclusion of health losses and additional costs associated with patients losing the ability to sit without support.

Table 3 summarises the main aspects of the company's current model, the original model[9] and the post-ACD model[6] for the later onset population. As shown in the table, many key aspects of the later onset model have changed considerably since the beginning of the appraisal.

Table 3: Main aspects of the company's later onset model – original model, post-ACD model and current model

Model element	Original model presented in CS[9]	Post-ACD model[6]	New model[8]
Structure	Single homogenous population represented by time-dependent transition matrices, except for separate matrix applied to patients discontinuing nusinersen treatment following post-scoliosis surgery. Nusinersen-treated patients cannot lose milestones; BSC patients cannot gain milestones.	Modelled using 7 sub-models of patients who are "improvers", "plateauers" or "worseners" with additional separate sub-models for those discontinuing nusinersen treatment post-scoliosis surgery. Plateauer sub-models redundant. Nusinersen-treated patients cannot lose milestones, except for arbitrary 1% of improvers who worsen and discontinue each cycle; BSC patients cannot gain milestones.	Modelled using 7 sub-models of patients who are "improvers", "plateauers" or "worseners" with additional separate sub-models for those discontinuing nusinersen treatment post-scoliosis surgery. Plateauer sub-models are activated at fixed timepoints (after months 15 and 27, depending on state). Nusinersen-treated patients can improve, plateau or worsen at various timepoints (see Figure 2); BSC patients cannot gain milestones. Additional notional state of loss of ability to sit included by applying lower patient utilities, lower caregiver utilities and higher costs to the proportion of patients in state [i] (sits without support but does not roll) who have lost this milestone.
Survival	Flexible spline model (2-knots) based on Zerres *et al*[10] and general population life tables.[13] Mortality adjustment factor of 0.50 applied to nusinersen group in states consistent with Type 3 SMA (states [v] to [vi]). The application of this adjustment factor means that patients in these states are apportioned 50% of the improved survival probability and 50% of the worse survival probability.	Flexible spline model (2-knots) based on Zerres *et al*[10] and general population life tables.[10] No difference in mortality risk between better and worse health states. Overall survival assumed to be identical for nusinersen and BSC.	Flexible spline model (2-knots) based on Zerres *et al*[10] and general population life tables.[10] Mortality adjustment factor of 0.75 applied to nusinersen group in states consistent with Type 3 SMA (states [v] to [vi]). The application of this adjustment factor means that patients in these states are apportioned 75% of the improved survival probability and 25% of the worse survival probability.

Model element	Original model presented in CS[9]	Post-ACD model[6]	New model[8]
Transition probabilities (observed period)	Both groups - patient count data from CHERISH,[11] days 1-456	Same as original model	Same as original model
Transition probabilities (extrapolation period)	Each group uses arm-specific HFMSE thresholds from CHERISH[11] Nusinersen group - mean rate of improvement from CHERISH ([redacted] points per month) BSC group - mean rate of worsening from CHERISH ([redacted] points per month)	Both groups use same HFMSE thresholds from CHERISH[11] Improvers - mean rate of improvement from CHERISH ([redacted] points per month) Worseners (and BSC group) - mean rate of worsening from CHERISH ([redacted] points per month)	Both groups use same HFMSE thresholds from CHERISH[11] Improvers - mean rate of improvement from CHERISH ([redacted] points per month). Additional probability of worsening by one health state whilst remaining an improver based on weighted average across timepoints from CHERISH ([redacted]) Plateauers – no transitions allowed between states. Proportion of patients becoming worseners (those who do not plateau) based on CHERISH.[11] Plateau assumed to occur at 5 or 6 years of age depending on health state, based on clinical opinion received by the company. Worseners (and BSC group) - mean rate of worsening from CHERISH ([redacted] points per month)
Scoliosis surgery	Non-ambulant patients – 43% at 12 years Ambulant patients – 43% at 15 years 20% patients discontinue nusinersen after surgery	Same as original model	Non-ambulant patients – 60% at 6 years Ambulant patients – 60% at 12 years 20% patients discontinue nusinersen after surgery
Modelled nusinersen stopping rule(s)	Patients discontinue if: (a) no milestones are achieved by end of month 15, or (b) patient cannot receive nusinersen treatment following scoliosis surgery	Patients discontinue if: (a) no milestones are achieved by end of month 15, (b) patient cannot receive nusinersen treatment following scoliosis surgery, or (c) patient becomes a worsener	Patients discontinue if: (a) no milestones are achieved by end of month 15, (b) patient cannot receive nusinersen treatment following scoliosis surgery, or (c) patient becomes a worsener (note - patients can in principle repeatedly worsen whilst still being classed as an improver)

Model element	Original model presented in CS[9]	Post-ACD model[6]	New model[8]
Health state costs	Based on milestones associated with SMA types from Bastida *et al*[15]	Based on milestones associated with SMA types from Biogen RWE survey[6]	Based on milestones associated with SMA types from Biogen RWE survey (weighted average of estimates from GOSH and Newcastle Trust only). Type I SMA cost doubled. Cost associated with loss of ability to sit based on costs for SMA Type I used in company's current early onset model (estimated value doubled).
Patient utilities	PedsQL data from CHERISH mapped to EQ-5D[9]	EQ-5D vignette study (Lloyd *et al*[16])	Company's experts' HRQoL estimates[8] (not preference-based) Utility associated with loss of ability to sit based on HRQoL for state [iii] (moderate milestones) in current early onset model.
Caregiver utilities	Based on Bastida *et al*[15] plus multiple assumptions linking caregiver utility to patient utility 1 caregiver assumed	"Wide range" utilities based on range defined by mean utility from Spanish caregiver subgroup in Bastida *et al*[15] (worst state) and general population utility (best state) 2 caregivers assumed	"Wide range" utilities based on range defined by mean utility from Spanish caregiver subgroup in Bastida *et al*[15] (worst state) and general population utility (best state). Utilities for states [i] to [iii] amended for consistency with early onset model. 3 caregivers assumed for patients who lose ability to sit. 2 caregivers assumed for all other patients.
PAS / access proposal	Simple price discount ([redacted] reduction from list price) proposed prior to first Appraisal Committee meeting	Complex agreement combined with price discount ([redacted] reduction from list price)	Simple price discount ([redacted] reduction from list price). [redacted]

2.2.3 Company's current model results – later onset population

Table 4 presents the results of the company's base case analysis and additional sensitivity analyses for the later onset population (including the proposed PAS). Based on the deterministic version of the model, the base case ICER including only patient health gains is estimated to be [redacted] per QALY gained. The lowest ICER (including patient health gains) generated from the company's sensitivity analyses is [redacted] per QALY gained (company's analysis S14 - disease duration <25 months subgroup), whilst the highest ICER is [redacted] per QALY gained (company's analysis S15 - disease duration ≥25 months subgroup). When caregiver health losses are also included in the model, the deterministic base case ICER is estimated to be [redacted] per QALY gained. The lowest ICER (including patient and caregiver QALY losses) generated from the company's sensitivity analyses is [redacted] per QALY gained (company's analysis S14 - disease duration <25 months subgroup), whilst the highest ICER is [redacted] per QALY gained (company's analysis S15 - disease duration ≥25 months subgroup).

With respect to the company's results for the later onset population, the ERG notes the following:

- The company's addendum[8] includes a useful range of sensitivity analyses which test the importance of many of the key uncertainties in the model.
- The current later onset model estimates a gain in survival for nusinersen versus BSC of 1.81 years; however, this is not a key driver of cost-effectiveness. Rather, the ICERs are more sensitive to assumptions which influence the amount of time that patients spend in particular health states and the HRQoL impacts and costs associated with these.
- The inclusion of an assumption that patients can lose the ability to sit has an important impact on the model results. Whilst patients can lose the ability to sit in both groups, this only applies to "worseners" who are no longer receiving, or have never received, nusinersen. When this factor is removed from the analysis, the ICER for nusinersen versus BSC (patient health gains only) is increased to [redacted] per QALY gained (company's analysis S9). This is therefore a key addition within the company's current model.
- The model results are sensitive to the time at which the improvement plateau is applied; delaying the time of the plateau by one year reduces the ICER (patient health gains only) to [redacted] per QALY gained (company's analysis S4). Conversely, assuming that the plateau occurs after 15 months for all states increases the ICER to [redacted] per QALY gained (ERG analysis not shown in table). Removing the assumption of plateau altogether leads to a situation in which nusinersen dominates BSC (note – this finding only holds when the assumptions regarding losing sitting ability are also included).
- The ICER for nusinersen versus BSC is considerably improved for patients with a shorter disease duration (company's analyses S14 and S15: <25 months ICER = [redacted] versus ≥25

months ICER = [redacted] per QALY gained). This difference is much more pronounced within the current model than for previous iterations of the model.[6, 9]

- In contrast to the company's current early onset model, the inclusion of caregiver health losses in the analysis advantages nusinersen in the later onset population. This is because survival is broadly similar between the treatment groups, but patients in the nusinersen group are assumed to have comparably better motor function and therefore a reduced caregiver burden. As with the company's post-ACD model,[8] the model predicts that for each patient receiving nusinersen, the drug will lead to more incremental health gain for caregivers than for the patient. The inclusion of three caregivers for those patients who lose the ability to sit further increases the incremental caregiver QALY gain for nusinersen versus BSC.

Table 4: Company's current model results – later onset population (adapted from company's addendum[8])

Option	QALYs (patient)	QALYs (caregivers)	Cost	Inc. QALYs (patient)	Inc. QALYs (caregivers)	Inc. cost	ICER (patient)	ICER (patient+ caregivers)
Revised model base case								
Nusinersen	8.75	-9.02	[redacted]	2.56	3.38	[redacted]	[redacted]	[redacted]
BSC	6.19	-12.40	[redacted]	-	-	-	-	-
S1 – Slower BSC arm decline in HFMSE (Kaufmann *et al*[19])								
Nusinersen	8.82	-8.89	[redacted]	2.53	3.33	[redacted]	[redacted]	[redacted]
BSC	6.29	-12.22	[redacted]	-	-	-	-	-
S2 – Mortality adjustment factor for better health states = 0.5								
Nusinersen	8.57	-9.02	[redacted]	2.40	3.38	[redacted]	[redacted]	[redacted]
BSC	6.17	-12.40	[redacted]	-	-	-	-	-
S3 – Mortality adjustment factor for better health states = 1.0								
Nusinersen	9.05	-9.03	[redacted]	2.82	3.38	[redacted]	[redacted]	[redacted]
BSC	6.22	-12.41	[redacted]	-	-	-	-	-
S4 – Improvement plateau applied 1 year later								
Nusinersen	10.39	-8.17	[redacted]	4.19	4.24	[redacted]	[redacted]	[redacted]
BSC	6.19	-12.40	[redacted]	-	-	-	-	-
S5 – Proportion of improvers who can worsen and subsequently improve doubled ([redacted])								
Nusinersen	8.65	-9.08	[redacted]	2.46	3.32	[redacted]	[redacted]	[redacted]
BSC	6.19	-12.40	[redacted]	-	-	-	-	-
S6 – Proportion of improvers who can worsen and subsequently improve halved ([redacted])								
Nusinersen	8.81	-8.99	[redacted]	2.62	3.41	[redacted]	[redacted]	[redacted]
BSC	6.19	-12.40	[redacted]	-	-	-	-	-
S7 – Proportion of patients who discontinue per cycle based on last observed assessment without adjustment*								
Nusinersen	8.96	-8.74	[redacted]	2.77	3.67	[redacted]	[redacted]	[redacted]
BSC	6.19	-12.40	[redacted]	-	-	-	-	-
S8 – Proportion of patients who worsen and discontinue at age 5/6 years doubled								
Nusinersen	8.45	-9.47	[redacted]	2.26	2.93	[redacted]	[redacted]	[redacted]
BSC	6.19	-12.40	[redacted]	-	-	-	-	-
S9 – Patients do not lose the ability to sit without support								
Nusinersen	10.04	-6.35	[redacted]	1.62	1.42	[redacted]	[redacted]	[redacted]
BSC	8.43	-7.77	[redacted]	-	-	-	-	-

Option	QALYs (patient)	QALYs (caregivers)	Cost	Inc. QALYs (patient)	Inc. QALYs (caregivers)	Inc. cost	ICER (patient)	ICER (patient+ caregivers)
S10 – Health state costs adjustment factor for type I (1.5)								
Nusinersen	8.75	-9.02	[redacted]	2.56	3.38	[redacted]	[redacted]	[redacted]
BSC	6.19	-12.40	[redacted]	-	-	-	-	-
S11 – ERG clinical advisors' patient HRQoL (including ERG valuation of early onset SMA moderate milestones HRQoL for patients losing ability to sit)								
Nusinersen	11.28	-9.02	[redacted]	2.04	3.38	[redacted]	[redacted]	[redacted]
BSC	9.24	-12.40	[redacted]	-	-	-	-	-
S12 – 'Narrow range' caregiver utilities (UK subgroup from Bastida *et al* - including 'narrow range' valuation of early onset caregiver utility for patients losing ability to sit)								
Nusinersen	8.75	-6.94	[redacted]	2.56	2.05	[redacted]	[redacted]	[redacted]
BSC	6.19	-9.00	[redacted]	-	-	-	-	-
S13 – 1 caregiver assumed for Type II/III SMA (2 caregivers assumed for patients losing ability to sit)								
Nusinersen	8.75	-5.39	[redacted]	2.56	2.33	[redacted]	[redacted]	[redacted]
BSC	6.19	-7.73	[redacted]	-	-	-	-	-
S14 – Subgroup < 25 months disease duration								
Nusinersen	10.79	-6.78	[redacted]	4.78	5.95	[redacted]	[redacted]	[redacted]
BSC	6.01	-12.73	[redacted]	-	-	-	-	-
S15 – Subgroup ≥25 months disease duration								
Nusinersen	8.23	-9.36	[redacted]	0.73	1.07	[redacted]	[redacted]	[redacted]
BSC	7.50	-10.44	[redacted]	-	-	-	-	-

** The ERG was unable to implement this sensitivity analysis using the company's model*

3. ERG verification of company's current models and commentary on latest model amendments

3.1 Verification of company's current models

As discussed in the ERG's critique of the company's response to the ACD,[7] the company's early and later onset post-ACD models were large and complex. These previous versions of the models each used seven sub-models to account for patients who improve, plateau, or worsen before or after scoliosis surgery, with mixing between the sub-models to account for patients discontinuing nusinersen treatment as a consequence of losing efficacy and/or undergoing scoliosis surgery. The inclusion of this mixing across sub-models necessitated the tracking of new and existing patients in each sub-model which further increased the complexity of the overall model implementation. Within the post-ACD models, the "plateauer" sub-models were redundant, as patients receiving treatment with nusinersen were assumed to continually improve unless they discontinued treatment with nusinersen.

The company's current models[8] feature an additional level of complexity in that the plateauer sub-models have been activated; consequently, there is more mixing between sub-models in the current models compared with the post-ACD models.[6] Given this complexity, the ERG considered that a comprehensive verification of the current models by checking the formulae contained within individual cells was not feasible within the available timescales. Instead, the ERG double-programmed both of the company's current models. The ERG's rebuilt models were streamlined by condensing the overall structure into two sub-models: "improvers/plateauers (on treatment)" and "worseners (discontinued"). Time-dependent transition matrices were used within the "improvers/plateauers (on treatment)" sub-model to account for patients who stop improving and plateau at specific timepoints, and post-scoliosis outcomes were handled by raising the probability of entering the "worseners (discontinued)" sub-model at the timepoints at which scoliosis surgery is assumed to occur. The same approach was taken within the rebuilt models for both the early and later onset populations.

Table 5 and Table 6 summarise the results of the ERG's double-programming exercise for the early onset and later onset models, respectively. As shown in the tables, the results from the company's current models and the ERG's rebuilt models are similar within both the early and later onset populations. The ERG notes that there is a discrepancy between the ICERs which include patient health gains and caregiver QALY losses for the early onset population (company's model ICER = [redacted] per QALY gained; ERG's rebuilt model ICER = [redacted] per QALY gained). It is possible that either early onset model is subject to a programming error. However, the ERG does not believe that resolving this error, if it exists, would have a significant influence the overall conclusions drawn from the economic analysis.

Table 5: Results of the company's current early onset model and the ERG's double-programmed early onset model (including PAS)

Early onset model				
Model outcome	**Company's new model**		**ERG's rebuilt model**	
	Nusinersen	**BSC**	**Nusinersen**	**BSC**
LYGs (undiscounted)	8.50	2.14	8.56	2.14
QALYs (patients, discounted)	2.64	0.00	2.74	0.00
QALYs (caregivers, discounted)	-4.48	-2.61	-4.32	-2.51
Costs (discounted)	[redacted]	[redacted]	[redacted]	[redacted]
ICER (patients)	[redacted]	-	[redacted]	-
ICER (patients + caregivers)	[redacted]	-	[redacted]	-

Table 6: Results of the company's current later onset model and the ERG's double-programmed early onset model (including PAS)

Later onset model				
Model outcome	**Company's new model**		**ERG's rebuilt model**	
	Nusinersen	**BSC**	**Nusinersen**	**BSC**
LYGs (undiscounted)	38.48	36.67	38.52	36.67
QALYs (patients, discounted)	8.75	6.19	8.96	6.30
QALYs (caregivers, discounted)	-9.02	-12.40	-9.02	-12.57
Costs (discounted)	[redacted]	[redacted]	[redacted]	[redacted]
ICER (patients)	[redacted]	-	[redacted]	-
ICER (patients + caregivers)	[redacted]	-	[redacted]	-

As noted in the footnotes to Table 2, the ERG was able to replicate the results of all but two of the analyses presented in the company's addendum (company's analysis S7 - Proportion of patients who discontinue per cycle based on last observed assessment without adjustment") using the company's models. The ERG was also able to replicate most of the company's sensitivity analyses using the ERG's rebuilt models without major discrepancies, although the ICER including caregiver QALY losses remained noticeably different across all analyses.

Overall, the ERG is broadly satisfied that the models appear to have been implemented without significant error.

3.2 ERG's comments on the company's model amendments

This section provides a brief commentary and critique of the company's current early and later onset models. In order to aid this process, the ERG sought the views of one of the clinical advisors who provided advice during the preparation of the ERG report.

3.2.1 Early onset model

Model structure and impact on predictions of patients reaching milestones – ERG comments

The ERG is broadly satisfied with the structural amendments to the early model which apply an assumption of an improvement plateau for all patients remaining on nusinersen treatment at particular

timepoints; this assumption constrains the proportion of patients who can reach the better health states. The company's addendum[8] states that the inclusion of this assumption is aligned with clinical opinion:

"Clinical expert opinion mentioned it will be unlikely that patients that have not reached the ability to stand by 5 or 6 years will achieve it at a later age. Similarly, they believed that patients not reaching the ability to walk before their 6th or 7th birthdays will never achieve that ability." (Company's addendum,[8] page 12).

The ERG's clinical advisor agreed with the clinical advice received by the company on this point. However, the ERG notes that the implementation of the overall sub-model structure includes some questionable assumptions:

- Once classed as an "improver", a patient can only lose treatment benefit and discontinue nusinersen (i.e. become a "worsener") at the two timepoints at which the plateau assumption is applied. The post-ACD model[6] allowed worsening during each model cycle (albeit using an arbitrary value of 1%).
- When patients are improvers (whilst on treatment), they can improve, stay in the same state or worsen. The model allows these patients to repeatedly worsen, whilst still being classed as an improver and still remaining on treatment with nusinersen; however, the ERG notes that the probability that a patient loses two consecutive milestone categories is small.
- [redacted] This would require the inclusion of tunnel states and would further increase the complexity of the model.
- From the point at which patients are classed as "plateauers", they cannot subsequently lose milestones unless they discontinue nusinersen treatment due to scoliosis surgery, yet they could lose milestones when they were previously classed as an improver.

The impact of relaxing these assumptions is generally unclear and evidence to inform long-term treatment discontinuation is scant.

The inclusion of the improvement plateau in the current model is more conservative than the previous iterations of the model[6, 9] (both of which assumed an indefinite ongoing improvement in motor milestones for all patients who remain on treatment with nusinersen). The ERG notes that the proportion of patients reaching the best health states is also influenced by the rate of improvement in CHOP INTEND score; the rate of improvement applied in the current model is markedly lower than that applied within previous iterations of the model (current model = [redacted] points; previous models = [redacted]

points). Personal communication from the company indicates that this rate of improvement in CHOP INTEND was based on [redacted] patients. Within the company's current early onset model, the maximum percentage of patients initiating treatment with nusinersen who ever reach state [vi] (walks with support) or state [vii] (stands/walks unaided) is estimated to be 16.3% (see Appendix 1, Figure 3). This is considerably lower than the percentage of patients reaching these states in previous iterations of the company's model (percentage of initial cohort reaching the best two health states: original model[9] = 58.2%; post-ACD model[6] = 30.9%). The ERG's advisor stated that the proportion of patients reaching the two best health states in the current early onset model was probably reasonable.

The ERG considers that there remains considerable uncertainty regarding the extent to which nusinersen may enable patients to reach the milestone of walking unaided. In both ENDEAR[4] and the latest data-cut of SHINE,[5] no patients reached the milestones of walking with or without assistance. The ERG's clinical advisor noted that this may be a consequence of the short timescales of the clinical studies; the advisor also highlighted that within the Expanded Access Programme for nusinersen, some patients have reached the states of walking with assistance. The ERG believes that the only current evidence supporting the notion that nusinersen can enable patients with early onset SMA to achieve the milestone of walking independently is from Study CS3A;[14] [redacted] Therefore, whilst there is some, albeit limited, evidence that patients can reach these better milestones, the proportion of patients who will achieve these in clinical practice is currently unknown.

Transition probability parameters – ERG comments

The ERG considers that the inclusion of longer-term patient count data from SHINE[5] is reasonable. The ERG notes that the available data for the nusinersen group beyond month 22 are limited (n=[redacted], with further attrition at later visits) and no additional longer-term data are available for the BSC group of the model.

Despite the ERG's concerns regarding the permitted transitions for improvers, plateauers and worseners described above, the ERG agrees that the company's inclusion of a probability of worsening whilst patients are receiving nusinersen is reasonable (probability = [redacted]).

The ERG considers it reasonable to use ENDEAR[4] and SHINE[5] to inform the rate of increase in CHOP INTEND for the nusinersen group; this rate is applied to thresholds which define whether the patient is in the current state or the next best/worst health state (described in the ERG report,[20] page 121). As noted above, the rate of improvement applied in the current model is considerably lower than that assumed in previous iterations of the model. Together with the inclusion of the assumption of an improvement plateau, this limits the expected health gains achieved in the nusinersen group.

Survival assumptions – ERG comments

The modelled survival projections derived from the company's current early onset model are shown in Appendix 1, Figure 4. The company's current model produces mean survival estimates of 8.50 years for nusinersen and 2.14 years for BSC (incremental survival gain = 6.36 years).

The ERG's clinical advisor believed that it is reasonable to include an improved survival prognosis for patients reaching milestones which are consistent with Type 2/3 SMA. The ERG notes that the company's clinical advisors suggested a wide range of mortality adjustment factors of 0.50 to 1.00; this suggests considerable uncertainty.

The ERG has some concerns regarding the validity of the company's approach to survival modelling and notes that the approach which involves apportioning mortality risk from two separate survival functions is unconventional. In addition, the use of an HR which is subsequently tapered is inconsistent with the assumption of proportional hazards; it is unclear why this approach has been taken if the underlying assumption is not considered to be appropriate. In addition, the company has extended the duration over which the HR is tapered (from 60 months in the post-ACD model to 120 months in the current model). No justification is provided for this amendment in the company's addendum on the current models,[8] and the inclusion of tapering of the HR was mentioned but not justified in the company's post-ACD response.[6] Despite these concerns, the ERG's clinical advisor believed that the overall mean survival estimates for both groups may be reasonable, and commented that predicted survival in the nusinersen group might be underestimated. The advisor also commented that in reality, one might expect the survival curves to drop more acutely and subsequently flatten out, thereby reflecting an initial phase with a high mortality rate, and a lower subsequent mortality hazard for those surviving beyond this point. The ERG's advisor also stated that better survival would be expected in patients who initiate treatment with nusinersen earlier compared with those who initiate treatment later.

The ERG believes that the expected survival gain for nusinersen versus BSC remains an important area of uncertainty.

Patient and caregiver HRQoL – ERG comments

The patient and caregiver utility/HRQoL values applied in the company's original model, the post-ACD model and the current model for the early onset population are shown in Table 9 and Table 10 in Appendix 2. As discussed in the ERG report,[20] the available preference-based utility estimates for SMA[9, 15, 16] are subject to face validity issues. As such, the ERG believes that it may be more reasonable to use HRQoL estimates based on clinical expert opinion in this case. However, the ERG highlights that some caution is required as: (i) these values are based on opinion rather than a formal elicitation of preferences for competing health states; (ii) the health states are defined only by level of motor function; (iii) different clinical advisors may suggest different valuations for the same health states, and (iv) there is a possibility that the values obtained from the experts may not reflect the views of people with SMA or their carers.

Prior to submission of the original ERG report,[20] the ERG's clinical advisors expressed considerable difficulty in providing reliable estimates of HRQoL for the model health states, and noted that expectations will be very different as children get older. With respect to the company's new analyses, the ERG's advisor believed that most of the company's current HRQoL estimates were reasonable, but that a value closer to 0.50 (rather than 0.40) would apply to health state [iv] (sits without support).

The ERG notes that the survey presented in the company's addendum suggests a significant caregiver burden. The ERG's clinical advisor noted that the caregiver burden for patients with significantly improved motor milestones may be less than that for patients not reaching these milestones. This is not reflected in the company's current early onset model and may improve the ICER for nusinersen slightly.

The company's current model uses a single value of caregiver HRQoL from the subgroup of Spanish caregivers included in the Bastida study;[15] this value is assumed to reflect caregiver utility for the worst health state (no milestones achieved). Caregiver utilities for the other health states are based on assumption that HRQoL increases uniformly for patients in each adjacent improved health state up to a maximum value based on the level of HRQoL in the general population. The ERG notes that any estimate of caregiver burden produced from the company's model should be interpreted with caution as the caregiver utility values are largely driven by assumptions rather than evidence.

Resource use and costs – ERG comments

The costs associated with SMA type used in the company's original model, the post-ACD model and the current model for the early onset population are shown in Table 11 in Appendix 2. The ERG believes that the RWE survey is a more appropriate source than the study reported by Bastida *et al.*[15] Within the company's current model, data from all centres except GOSH and Newcastle were excluded on the basis of clinical advice regarding the representativeness of the data. The company's experts further suggested that the costs for Type I SMA may be underestimated and that these values should be inflated by a factor of 2. The ERG's clinical advisor believed that doubling the costs for Type I SMA may still underestimate the true costs of managing the disease. The ERG notes that the Type I costs do not have a marked impact on the ICER within the early onset population, but do have a substantial impact on the ICER within the later onset population (see company's analyses presented in Table 4 and Table 5, and ERG's analyses presented in Table 6 and Table 7).

3.2.2 Later onset model

Model structure and impact on predictions of patients reaching milestones – ERG comments

The overall structural approach used in the company's current later onset model is similar to that used for the early onset model. The ERG's concerns regarding the permitted transitions for improvers, plateauers and worseners and mixing across sub-models in the early onset model also apply to the later onset model. Nonetheless, the inclusion of the assumed improvement plateau in the current later onset model is more conservative than previous iterations of the model[6, 9] (both of which assumed indefinite ongoing improvement in motor milestones for all patient who remain on nusinersen treatment). Within the company's current later onset model, the maximum percentage of patients initiating treatment with nusinersen who ever reach state [v] (stands unaided) or state [vi] (walks unaided) is estimated to be 14.4% (see Appendix 1, Figure 5). This is considerably lower than the percentage of patients reaching these states in previous versions of the company's model (probability of reaching stands unaided or walks unaided - original model 54.0%, post-ACD model 48.9%). This limits the expected health gains achieved in the nusinersen group.

The company's current later onset model also includes an assumption that patients who reach the sits without support state will eventually lose the ability to sit. This was not included in previous iterations of the model. The ERG's clinical advisor believed that this assumption is broadly reasonable, stating that 85-90% of Type 2/3 SMA patients are likely to lose this ability. The ERG notes that the inclusion of this factor is a key driver of the ICER for nusinersen versus BSC. Personal communication from the company stated that patients in CHERISH did not experience loss of sitting, mostly likely due to the short duration of the study, and that the omission of this event from the original model was not highlighted as a limitation during its clinical validation.

Transition probability parameters – ERG comments

Despite the ERG's concerns regarding the permitted transitions within each sub-model and mixing across sub-models, the ERG agrees that the company's inclusion of a probability of worsening whilst patients are receiving nusinersen is reasonable (probability = [redacted]).

Survival assumptions – ERG comments

The modelled survival projections derived from the company's current early onset model are shown in Appendix 5, Figure 6. The company's current model estimates mean survival estimates of 38.48 years for nusinersen and 36.67 years for BSC (incremental survival gain = 1.81 years).

The ERG's clinical advisor believed that the inclusion of an assumption of improved survival prognosis for patients reaching milestones consistent with Type 3 SMA was reasonable. As with the early onset model, the ERG notes that the company's clinical advisors suggested a wide range of mortality adjustment factors of 0.50 to 1.00; again, this suggests considerable uncertainty.

The ERG's clinical advisor believed that the company's new survival projections are probably reasonable.

Patient and caregiver HRQoL – ERG comments

The issues described above regarding HRQoL for the early onset model also apply to the later onset model.

The ERG's clinical advisor noted that it might be reasonable to distinguish between HRQoL for health states [i] (sits without support but does not roll), state [ii] (sits and rolls independently) and state [iii] (sits and crawls with hands and knees) on the basis of correlation with other markers of the disease (e.g. scoliosis and respiratory difficulties). However, the clinical advisor also noted that whilst these motor milestones are relevant in children, they become less relevant as patients get older.

The ERG's advisor believed that the assumed HRQoL value of 0.20 for patients who lose the ability to sit is reasonable.

The ERG's advisor also believed that the assumption that patients who lose the ability to sit will require additional caregiver support is appropriate. As with the early onset model, the ERG believes that any estimate of caregiver burden produced from the company's model should be interpreted with caution as the caregiver utility values are largely driven by assumptions rather than evidence.

Resource use and costs – ERG comments

The ERG has no additional comments relating specifically to the later onset model.

Scoliosis surgery assumptions – ERG comments

The ERG's clinical advisor believed that the company's amendments to the timing and proportion of patients undergoing scoliosis surgery were appropriate. The advisor also noted that for some patients, scoliosis surgery may occur at an earlier timepoint than that assumed in the company's current model.

4. Additional ERG analyses undertaken using the company's current early and later onset models

This section presents additional analyses which address additional concerns raised within the ERG's critique.

The ERG reiterates that the company's addendum includes a number of relevant analyses using the current models; the ERG's additional analyses should be in addition to, rather than in place of, the company's analyses.

The following additional analyses were undertaken by the ERG using the company's current models:

Early onset population – additional ERG analyses

- *ERG analysis E1:* 1% of plateauers worsen by one state during each cycle
- *ERG analysis E2:* 5% of plateauers worsen by one state during each cycle
- *ERG analysis E3:* Overall survival HR and mortality adjustment factor removed
- *ERG analysis E4:* All scoliosis surgery undertaken 24 months earlier
- *ERG analysis E5:* No patients reach milestone of walking unaided
- *ERG analysis E6:* HRQoL for sits without support set equal to 0.50
- *ERG analysis E7:* Number of caregivers required for patients in health states consistent with Type 2/3 SMA set equal to 2
- *ERG analysis E8:* All disease management costs doubled
- *ERG analysis E9:* SMA 1 cost doubled.

Later onset population – additional ERG analyses

- *ERG analysis L1:* 1% of plateauers worsen by one state during each cycle
- *ERG analysis L2:* 5% of plateauers worsen by one state during each cycle
- *ERG analysis L3:* Mortality adjustment factor removed (equal survival in both treatment groups)
- *ERG analysis L4:* Proportion of patients who lose ability to sit set equal to 85%
- *ERG analysis L5:* All scoliosis surgery undertaken 24 months earlier
- *ERG analysis L6:* Use of caregiver utilities from the company's post-ACD model[6]

- *ERG analysis L7:* All disease management costs doubled
- *ERG analysis L8:* SMA 1 cost doubled.

The results of the ERG's additional analyses using the company's current early onset and later onset models are presented in Table 7 and Table 8, respectively.

Table 7: Results of ERG's additional analyses using the company's current early onset model

Option	QALYs (patient)	QALYs (caregivers)	Cost	Inc. QALYs (patient)	Inc. QALYs (caregivers)	Inc. cost	ICER (patient)	ICER (patient+ caregivers)
Company's base case								
Nusinersen	2.64	-4.48	[redacted]	2.64	-1.88	[redacted]	[redacted]	[redacted]
BSC	0.00	-2.61	[redacted]	-	-	-	-	-
***ERG analysis E1:* 1% of plateauers worsen by one state during each cycle**								
Nusinersen	2.52	-4.50	[redacted]	2.52	-1.90	[redacted]	[redacted]	[redacted]
BSC	0.00	-2.61	[redacted]	-	-	-	-	-
***ERG analysis E2:* 5% of plateauers worsen by one state during each cycle**								
Nusinersen	2.15	-4.55	[redacted]	2.15	-1.95	[redacted]	[redacted]	[redacted]
BSC	0.00	-2.61	[redacted]	-	-	-	-	-
***ERG analysis E3:* Overall survival HR and mortality adjustment factor removed**								
Nusinersen	0.98	-3.08	[redacted]	0.98	-0.47	[redacted]	[redacted]	[redacted]
BSC	0.00	-2.61	[redacted]	-	-	-	-	-
***ERG analysis E4:* All scoliosis surgery undertaken 24 months earlier**								
Nusinersen	2.62	-4.49	[redacted]	2.61	-1.88	[redacted]	[redacted]	[redacted]
BSC	0.00	-2.61	[redacted]	-	-	-	-	-
***ERG analysis E5:* No patients reach milestone of walking unaided**								
Nusinersen	2.59	-4.59	[redacted]	2.59	-1.99	[redacted]	[redacted]	[redacted]
BSC	0.00	-2.61	[redacted]	-	-	-	-	-
***ERG analysis E6:* HRQoL for sits without support set equal to 0.50**								
Nusinersen	2.81	-4.48	[redacted]	2.81	-1.88	[redacted]	[redacted]	[redacted]
BSC	0.00	-2.61	[redacted]	-	-	-	-	-
***ERG analysis E7:* Number of caregivers required for patients in health states consistent with Type 2/3 SMA set equal to 2**								
Nusinersen	2.64	-3.90	[redacted]	2.64	-1.30	[redacted]	[redacted]	[redacted]
BSC	0.00	-2.60	[redacted]	-	-	-	-	-
***ERG analysis E8:* All disease management costs doubled**								
Nusinersen	2.64	-4.48	[redacted]	2.64	-1.88	[redacted]	[redacted]	[redacted]
BSC	0.00	-2.61	[redacted]	-	-	-	-	-
***ERG analysis E9:* SMA 1 cost doubled**								
Nusinersen	2.64	-4.48	[redacted]	2.64	-1.88	[redacted]	[redacted]	[redacted]
BSC	0.00	-2.61	[redacted]	-	-	-	-	-

Table 8: Results of ERG's additional analyses using the company's current later onset model

Option	QALYs (patient)	QALYs (caregivers)	Cost	Inc. QALYs (patient)	Inc. QALYs (caregivers)	Inc. cost	ICER (patient)	ICER (patient+ caregiver)
Company's base case								
Nusinersen	8.75	-9.02	[redacted]	2.56	3.38	[redacted]	[redacted]	[redacted]
BSC	6.19	-12.40	[redacted]	-	-	-	-	-
ERG analysis L1: **1% of plateauers worsen by one state during each cycle**								
Nusinersen	8.15	-9.76	[redacted]	1.95	2.64	[redacted]	[redacted]	[redacted]
BSC	6.19	-12.40	[redacted]	-	-	-	-	-
ERG analysis L2: **5% of plateauers worsen by one state during each cycle**								
Nusinersen	6.97	-11.29	[redacted]	0.78	1.11	[redacted]	[redacted]	[redacted]
BSC	6.19	-12.40	[redacted]	-	-	-	-	-
ERG analysis L3: **Mortality adjustment factor removed (equal survival in both treatment groups)**								
Nusinersen	8.31	-9.01	[redacted]	2.19	3.38	[redacted]	[redacted]	[redacted]
BSC	6.12	-12.39	[redacted]	-	-	-	-	-
ERG analysis L4: **Proportion of patients who lose ability to sit set equal to 85%**								
Nusinersen	8.89	-8.70	[redacted]	2.47	3.15	[redacted]	[redacted]	[redacted]
BSC	6.42	-11.85	[redacted]	-	-	-	-	-
ERG analysis L5: **All scoliosis surgery undertaken 24 months earlier**								
Nusinersen	8.73	-9.06	[redacted]	2.54	3.34	[redacted]	[redacted]	[redacted]
BSC	6.19	-12.40	[redacted]	-	-	-	-	-
ERG analysis L6: **Use of caregiver utilities from the company's post-ACD model[6]**								
Nusinersen	8.75	-12.30	[redacted]	2.56	3.32	[redacted]	[redacted]	[redacted]
BSC	6.19	-15.61	[redacted]	-	-	-	-	-
ERG analysis L7: **All disease management costs doubled**								
Nusinersen	8.75	-9.02	[redacted]	2.56	3.38	[redacted]	[redacted]	[redacted]
BSC	6.19	-12.40	[redacted]	-	-	-	-	-
ERG analysis L8: **SMA 1 cost doubled**								
Nusinersen	8.75	-9.02	[redacted]	2.56	3.38	[redacted]	[redacted]	[redacted]
BSC	6.19	-12.40	[redacted]	-	-	-	-	-

Early onset model – results of additional ERG analyses

With respect to the ERG's additional exploratory analyses using the company's current early onset model, the ERG notes the following:

- When only patient health gains are included in the analysis, the lowest ICER remains in excess of [redacted] per QALY gained (ERG analysis E6 - HRQoL for sits without support set equal to 0.50). The highest ICER is estimated to be [redacted] per QALY gained (ERG analysis E8 - all disease management costs doubled).
- The inclusion of a probability that plateauers worsen by one state during each cycle (without leaving the plateauer sub-models) increases the ICER; however, the ERG notes that the values applied in these analyses are arbitrary.
- Removing the estimated survival benefits for nusinersen within the extrapolated period (ERG analysis E3) increases the ICER to [redacted] per QALY gained.
- Relative to the company's base case analysis, the ICER is increased (or maintained) across all but one of the ERG's additional analyses (ERG analysis E6 – HRQoL for sits without support equal to 0.50).
- When patient and caregiver health losses are included in the analysis, the lowest ICER is estimated to be [redacted] per QALY gained (ERG analysis E7 – two caregivers assumed for states consistent with Type 2/3 SMA). The highest ICER produced from these analyses is estimated to be [redacted] per QALY gained (ERG analysis E2 - 5% of plateauers worsen by one state during each cycle).

Later onset model – results of additional ERG analyses

With respect to the ERG's additional exploratory analyses using the company's current later onset model, the ERG notes the following:

- When only patient health gains are included in the analysis, [redacted] (ERG analyses L7 and L8). The ERG notes that these are extreme values. The highest ICER is estimated to be [redacted] per QALY gained (ERG analysis L2 - 5% of plateauers worsen by one state during each cycle); as noted above, this value is arbitrary. Assuming a lower probability of plateauers who worsen leads to lower ICERs (ERG analysis L1).
- Reducing the proportion of patients who lose the ability to sit to 85% increases the ICER to [redacted] per QALY gained (ERG analysis L4).
- Removing the mortality adjustment factor (thereby assuming equal survival for both treatment groups) has a negligible impact on the ICER (ERG analysis L4 - ICER = [redacted] per QALY gained).

- When only patient health gains are included, the ICER is generally stable across the other remaining exploratory analyses.
- When patient and caregiver health losses are included in the analysis, nusinersen remains dominant [redacted] (ERG analyses L7 and L8). The highest ICER produced from these analyses is estimated to be [redacted] per QALY gained (ERG analysis L2 - 5% of plateauers worsen by one state during each cycle). Assuming a lower probability of plateauers who worsen leads to lower ICERs (ERG analysis L1). The ICER appears to be broadly stable for the remaining analyses.

5. Conclusions

The company's amendments within the current versions of the early and later onset models take into account much of the advice suggested by the ERG regarding the extrapolation of treatment effects, the use of evidence and the incorporation of relevant clinical opinion within the model. The ERG notes that the structure, evidence sources and results of the company's early and later onset models have changed considerably over the course of the appraisal; the trajectories of motor milestone improvement and overall survival gains within the company's current early and later onset models are more conservative than those predicted by the original versions of these models.[9] The ERG's clinical advisor believed that the company's amendments to the models, and the predictions generated from them, are likely to be reasonable given current evidence. The company's current models include additional structural amendments which further increase their complexity. On the basis of the double-programming exercise presented in Section 3.1, the ERG is broadly satisfied that the company's models are not subject to programming errors which are significant enough to alter the conclusions drawn from the analyses.

The ERG has some remaining concerns regarding: (i) questionable structural assumptions regarding the time at which patients worsen and discontinue nusinersen treatment; (ii) the unconventional piecewise approach used to model overall survival in the early onset population; (iii) significant uncertainties regarding the durability of the effect of nusinersen treatment on motor function and overall survival; (iv) the costs of disease management, and (v) the HRQoL impacts of the disease on patients and their caregivers. These uncertainties should be borne in mind when interpreting the results of the analyses undertaken by the company and the ERG.

Summary of cost-effectiveness results for the early onset population – company's and ERG's analyses (including the current PAS)

Within the early onset population, the company's base case ICER for nusinersen versus BSC (including patient health gains) is estimated to be [redacted] per QALY gained. The sensitivity analyses undertaken by the company and the ERG produced ICERs which range from [redacted] (mortality adjustment factor

increased to 1.0) to [redacted] per QALY gained (disease management costs doubled). When caregiver health losses are also included, the company's base case ICER is estimated to be [redacted] per QALY gained. The analyses undertaken by the company and the ERG produced ICERs (including patient health gains and caregiver QALY losses) which range from [redacted] (number of caregivers = 1) to [redacted] per QALY gained (5% of plateauers worsen by one state during each cycle).

The ICER for nusinersen versus BSC within the early onset population remains consistently high as a consequence of extending survival with: (a) the assumption of a plateau in clinical improvement which limits the expected QALY gains, and (b) ongoing treatment and disease management costs which together lead to substantial lifetime costs for patients who, based on the model assumptions, would have otherwise died without nusinersen treatment. The ERG notes that under the assumption of a zero price for nusinersen, the ICERs are estimated to be [redacted] per QALY gained (patient health gains only) and [redacted] per QALY gained (patient health gains and caregiver QALY losses).

Summary of cost-effectiveness results for the later onset population - company's and ERG's analyses (including the current PAS)

Within the later onset population, the company's base case ICER (including patient health gains only) is estimated to be [redacted] per QALY gained. The sensitivity analyses undertaken by the company and the ERG produced ICERs ranging from [redacted] (Type 1 SMA/all disease management costs doubled) to [redacted] per QALY gained (5% plateauers worsen by one state during each cycle). When caregiver health losses are also included, the company's base case ICER is estimated to be [redacted] per QALY gained. The analyses undertaken by the company and the ERG produced ICERs (including patient health gains and caregiver QALY losses) which range from [redacted] (Type 1 SMA only or all disease management costs doubled) to [redacted] per QALY gained (5% of plateauers worsen by one state during each cycle).

The ERG notes that the assumption that without treatment with nusinersen, patients will lose the ability to sit, is a new addition which did not feature in previous iterations of the later onset model. The key drivers of the ICER in this population relate to the proportion of patients who lose the ability to sit, whether plateauing effects are maintained indefinitely (and if not, the rate at which patients lose milestones), the costs associated with managing SMA and disease duration.

[redacted]

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Appendix 1: Condensed Markov traces and overall survival projections derived from the company's current early and later onset models

Figure 3: Probability of reaching walks with assistance or stands/walks unaided – company's current early onset model

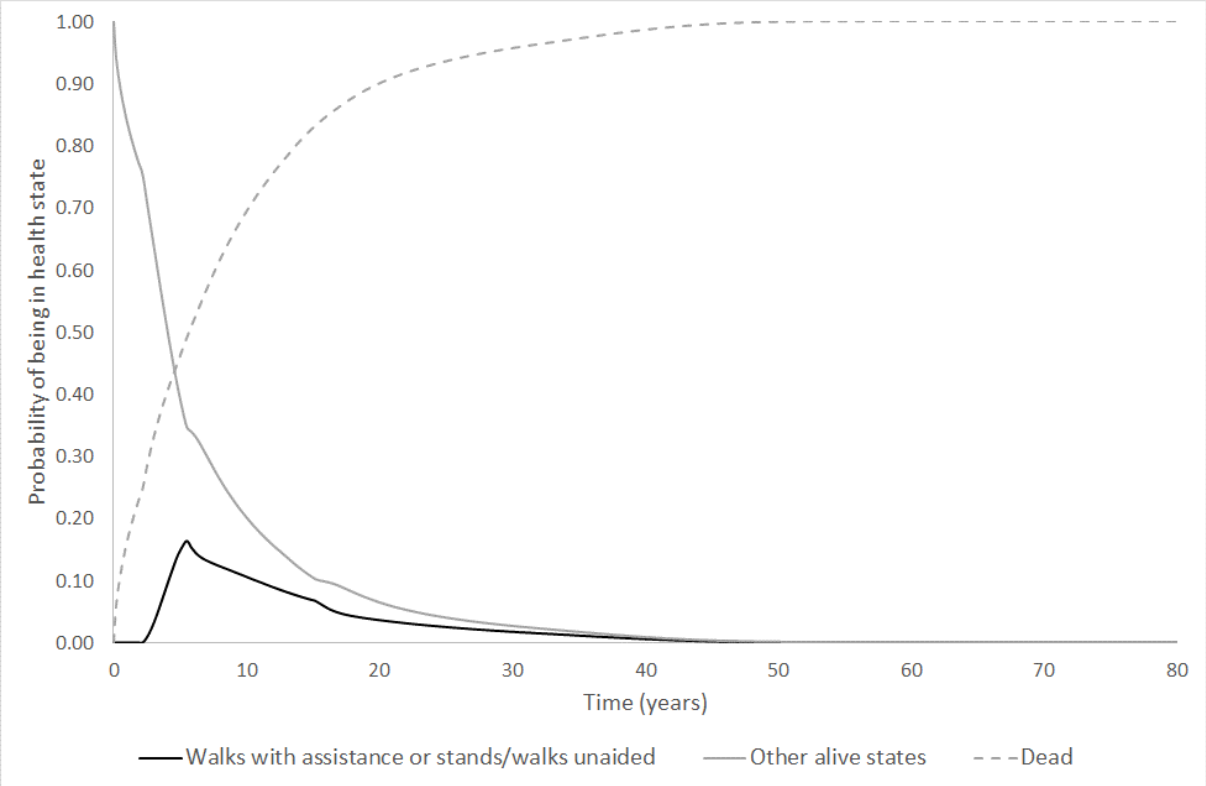


Figure 4: Modelled survival projection – company's current early onset model

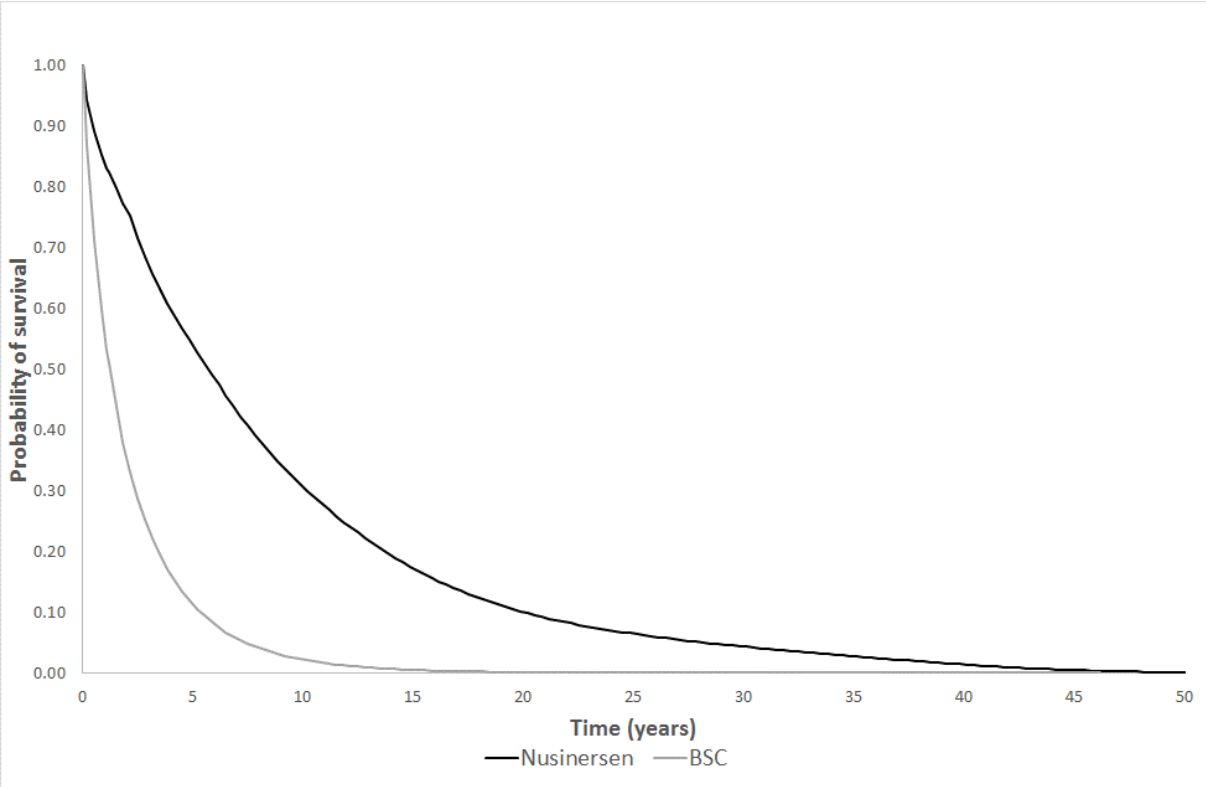


Figure 5: Probability of reaching walks with assistance or stands/walks unaided – company's current later onset model

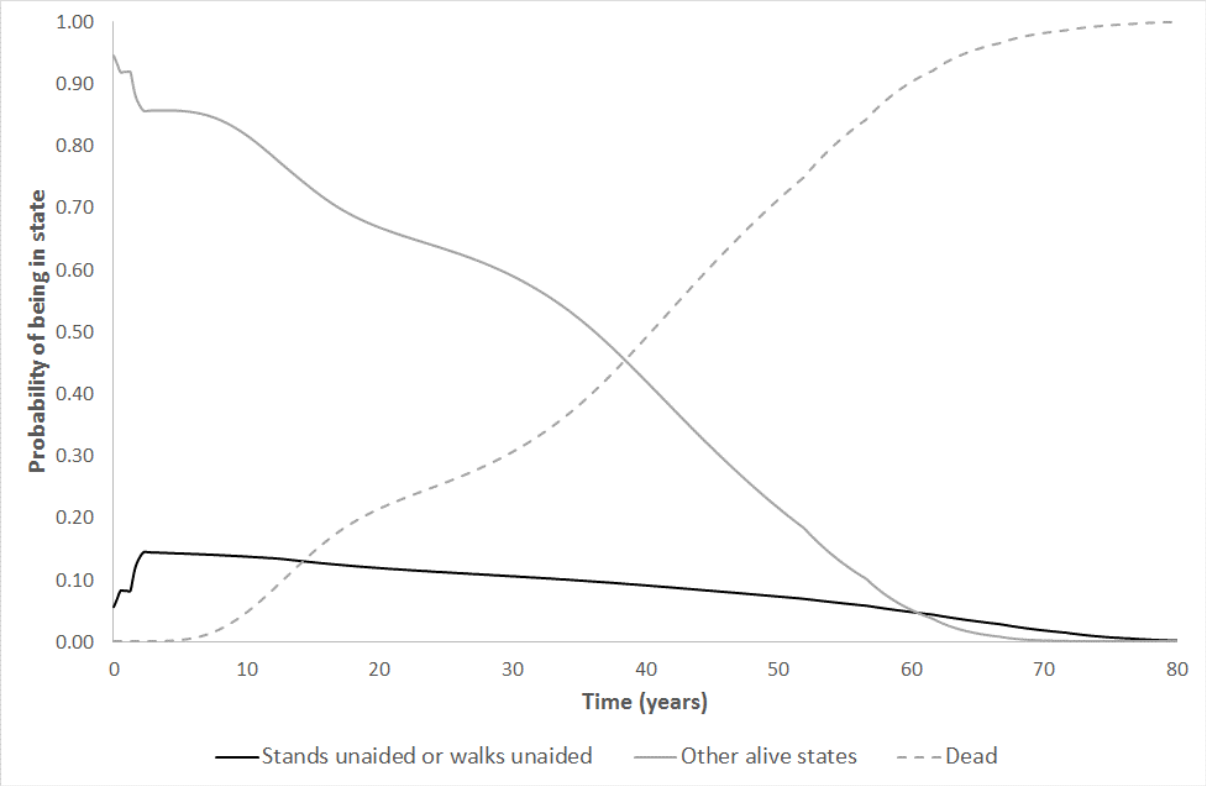
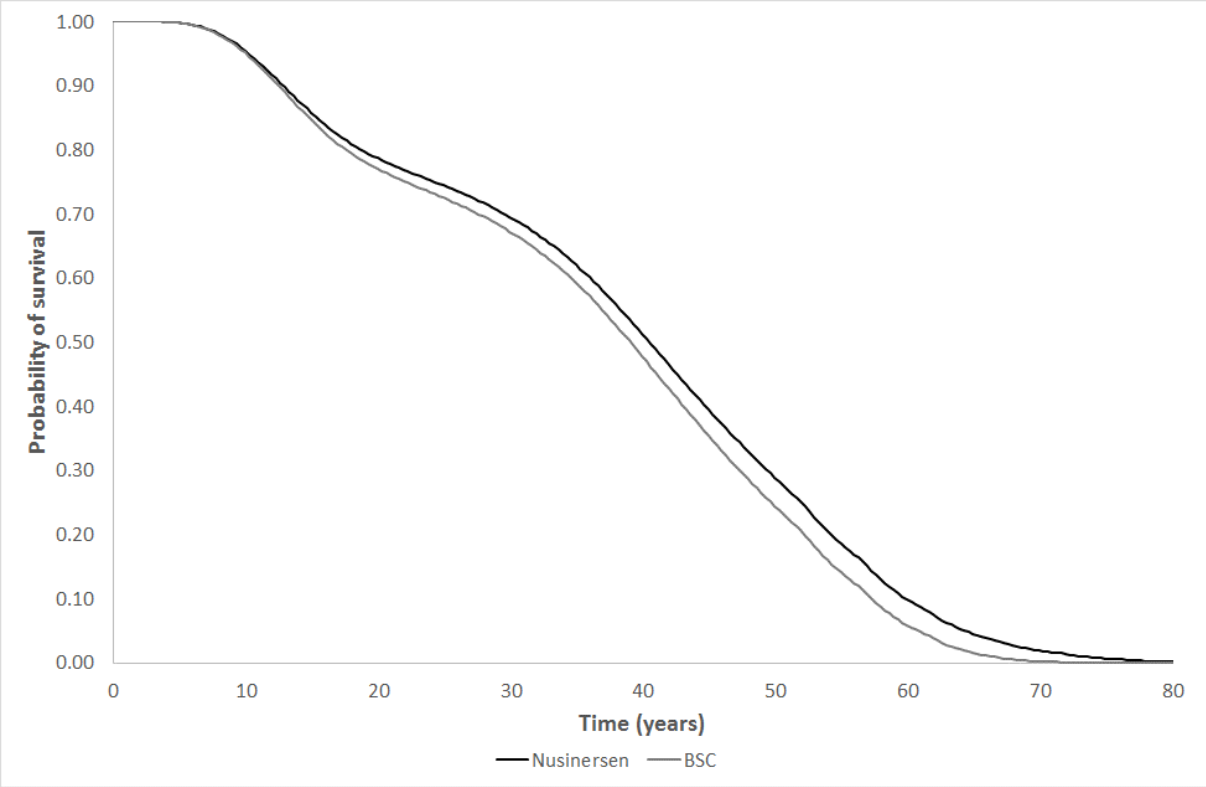


Figure 6: Modelled survival projection – company's current later onset model



Appendix 2: Updated HRQoL and cost data used the company's new models

Table 9: Patient utilities/HRQoL estimates applied in the company's original models, the post-ACD models and the current models

Patient utility values – early onset model			
Health state	**Original model - PedsQL mapping to EQ-5D[9]**	**Post-ACD model - EQ-5D vignette study (Lloyd *et al*[16])**	**Current model - company's experts' values[8]**
[i] No milestones achieved	0.733	-0.240	-0.020
[ii] Mild milestones	0.752	-0.120	0.100
[iii] Moderate milestones	0.752	-0.170	0.200
[iv] Sits without support	0.780	-0.040	0.400
[v] Stands with assistance	0.807	0.040	0.650
[vi] Walks with assistance	0.807	0.520	0.750
[vii] Stands/Walks unaided	0.878	0.710	0.850
Patient utility values – later onset model			
Health state	**Original model - PedsQL mapping to EQ-5D[9]**	**Post-ACD model - EQ-5D vignette study (Lloyd *et al*[16])**	**Current model - company's experts' values[8]**
[i] Sits without support but does not roll	0.733	0.040	0.400
[ii] Sits and rolls independently	0.752	0.040	0.450
[iii] Sits and crawls with hands and knees	0.780	0.100	0.500
[iv] Stands/Walks with assistance	0.807	0.390	0.700
[v] Stands unaided	0.807	0.720	0.850
[vi] Walks unaided	0.878	0.720	0.850

Table 10: Caregiver utilities applied in the company's original models, the post-ACD models and the current models

Caregiver utility values – early onset model			
Health state	**Original model[9] – Bastida *et al* plus assumptions linked to patient utility**	**Post-ACD model - Bastida *et al* (Spanish caregivers subgroup) plus assumptions**	**Post-ACD model - Bastida *et al* (Spanish caregivers subgroup) plus assumptions**
[i] No milestones achieved	0.832	0.484	0.484
[ii] Mild milestones	0.850	0.556	0.556
[iii] Moderate milestones	0.850	0.628	0.628
[iv] Sits without support	0.878	0.700	0.700
[v] Stands with assistance	0.905	0.771	0.771
[vi] Walks with assistance	0.905	0.843	0.843
[vii] Stands/Walks unaided	0.905	0.915	0.915
Caregiver utility values – later onset model			
Health state	**Original model[9] – Bastida *et al* plus assumptions linked to patient utility**	**Post-ACD model - Bastida *et al* (Spanish caregivers subgroup) plus assumptions**	**Post-ACD model - Bastida *et al* (Spanish caregivers subgroup) plus assumptions**
[i] Sits without support but does not roll	0.797	0.484	0.700
[ii] Sits and rolls independently	0.815	0.592	0.743
[iii] Sits and crawls with hands and knees	0.843	0.700	0.786
[iv] Stands/Walks with assistance	0.870	0.807	0.807
[v] Stands unaided	0.870	0.915	0.915
[vi] Walks unaided	0.941	0.915	0.915

Table 11: Health state costs applied in the company's original models, the post-ACD models and the current models

Health state costs– early onset model			
Health state	**Original model[9] - Bastida *et al*[15]**	**Post-ACD model – Company's RWE survey[6]**	**Post-ACD model – Company's RWE survey[8] (GOSH and Newcastle only), Type 1 costs doubled**
Type 1 SMA	[redacted]	£77,968	£148,214
Type 2 SMA	[redacted]	£55,185	£68,322
Type 3 SMA	[redacted]	£20,229	£21,765

Appendix 3: Summary of company's base case results across all submitted model versions (including price/access agreements at the time of each submission)

Table 12: Comparison of company's base case results for the early onset population across the original model, the post-ACD model and the current model

Model result	Original model[9]	Post-ACD model[6]	Current model[8]
PAS discount/access proposal			
Discounted price / vial	[redacted]	[redacted]	[redacted]
Additional access proposal elements	-	[redacted]	-
LYGs (undiscounted)			
Nusinersen	13.01	3.98	8.50
BSC	3.87	2.32	2.14
Incremental	**9.14**	**1.66**	**6.36**
Patient QALYs (discounted)			
Nusinersen	7.86	0.57	2.64
BSC	2.49	-0.48	0.00
Incremental	**5.37**	**1.05**	**2.64**
Net patient and caregiver QALYs (discounted)			
Nusinersen	7.61	-0.96	-1.84
BSC	2.17	-2.34	-2.60
Incremental	**5.44**	**1.37**	**0.76**
Costs (discounted)			
Nusinersen	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	[redacted]	[redacted]
Cost-effectiveness (incremental cost per QALY gained)			
Nusinersen vs BSC (patient QALYs)	[redacted]	[redacted]	[redacted]
Nusinersen vs BSC (patient +caregiver QALYs)	[redacted]	[redacted]	[redacted]

Table 13: Comparison of company's base case results for the later onset population across the original model, the post-ACD model and the current model

Model result	Original model[9]	Post-ACD model[6]	Current model[8]
PAS discount/access proposal			
Discounted price / vial	[redacted]	[redacted]	[redacted]
Additional access proposal elements	-	[redacted]	-
LYGs (undiscounted)			
Nusinersen	41.71	36.35	38.48
BSC	36.45	36.35	36.67
Incremental	**5.27**	**0.00**	**1.81**
Patient QALYs (discounted)			
Nusinersen	16.88	5.83	8.75
BSC	14.52	1.09	6.19
Incremental	**2.37**	**4.74**	**2.56**
Net patient and caregiver QALYs (discounted)			
Nusinersen	15.66	-3.56	-0.27
BSC	12.36	-14.30	-6.21
Incremental	**3.30**	**10.74**	**5.94**
Costs (discounted)			
Nusinersen	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	[redacted]	[redacted]
ICERs (incremental cost per QALY gained)			
Nusinersen vs BSC (patient QALYs)	[redacted]	[redacted]	[redacted]
Nusinersen vs BSC (patient +caregiver QALYs)	[redacted]	[redacted]	[redacted]

Appendix 4: Impact of current PAS within the each iteration of the company's models

Table 14: Current PAS applied to each iteration of the company's early onset model

Option	QALYs (patient)	QALYs (caregivers)	Cost	Inc. QALYs (patient)	Inc. QALYs (caregivers)	Inc. cost	ICER (patient)	ICER (patient+ caregivers)
Current PAS applied in company's current early onset model								
Nusinersen	2.64	-4.48	[redacted]	2.64	-1.88	[redacted]	[redacted]	[redacted]
BSC	0.00	-2.61	[redacted]	-	-	-	-	-
Current PAS applied in company's original early onset model[9]								
Nusinersen	7.86	-0.25	[redacted]	5.37	0.07	[redacted]	[redacted]	[redacted]
BSC	2.49	-0.32	[redacted]	-	-	-	-	-
Current PAS applied in company's post-ACD early onset model[6]								
Nusinersen	0.57	-1.54	[redacted]	1.05	0.32	[redacted]	[redacted]	[redacted]
BSC	-0.48	-1.86	[redacted]	-	-	-	-	-

Table 15: Current PAS applied to each iteration of the company's later onset model

Option	QALYs (patient)	QALYs (caregivers)	Cost	Inc. QALYs (patient)	Inc. QALYs (caregivers)	Inc. cost	ICER (patient)	ICER (patient+ caregivers)
Current PAS applied in company's current early onset model								
Nusinersen	8.75	-9.02	[redacted]	2.56	3.38	[redacted]	[redacted]	[redacted]
BSC	6.19	-12.40	[redacted]	-	-	-	-	-
Current PAS applied in company's original later onset model[9]								
Nusinersen	16.88	-1.22	[redacted]	2.37	0.93	[redacted]	[redacted]	[redacted]
BSC	14.52	-2.16	[redacted]	-	-	-	-	-
Current PAS applied in company's post-ACD later onset model[6]								
Nusinersen	5.83	-9.39	[redacted]	4.74	6.00	[redacted]	[redacted]	[redacted]
BSC	1.09	-15.38	[redacted]	-	-	-	-	-