NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Single Technology Appraisal

Risdiplam for treating spinal muscular atrophy in children and adults ID1631

Consultee and commentator comment form

Please use this form for submitting your comments on the draft remit, draft scope and provisional matrix of consultees and commentators. It is important that you complete and return this form even if you have no comments otherwise we may chase you for a response.

Enter the name of your organisation here: Spinal Muscular Atrophy UK (SMA UK)

Comments on the draft remit and draft scope

The draft remit is the brief for a proposed appraisal. Appendix B contains the draft remit. The draft scope, developed from the draft remit outlines the question that the proposed appraisal would answer.

Please submit your comments on the draft remit and draft scope using the table below. **Please take note of any questions that have been highlighted in the draft scope itself** (usually found at the end of the document).

If you have been asked to comment on documents for more than one proposed appraisal, please use a separate comment form for each topic, even if the issues are similar.

Please complete this form and upload it to NICE Docs by **Monday 24 February 2020**. If using NICE docs is not possible please return via email to scopingta@nice.org.uk If you have any questions please contact Michelle Adhemar, Project Manager on 44 (0)20 7045 2239 or at the email address above.

If you do not have any comments to make on the draft remit and draft scope, please state this in the box below.

Comment 1: the draft remit

Section	*Notes*	Your comments
Appropriateness	*It is important that appropriate topics are referred to NICE to ensure that NICE guidance is relevant, timely and addresses priority issues, which will help improve the health of the population. Would it be appropriate to refer this topic to NICE for appraisal?*	**Highly appropriate given the stage of development of this treatment:** **Clinical Trials and results:** Risdiplam is being studied in a broad clinical trial programme in SMA, with patients ranging from birth to 60 years old. One trial includes patients previously treated with SMA-targeting therapies. The clinical trial population represents the broad real-world spectrum of people living with this condition.

Section	*Notes*	Your comments
		October 2019 Roche's announced data for 45 patients enrolled in their JEWELFISH clinical trial for people aged 6 months-60 years who have previously participated in a trial with *SMN2*-targeting therapies, or **olesoxime**, or who received previous treatment with **nusinersen .** A sustained, greater than two-fold increase in median SMN protein versus baseline over 12 months of treatment was demonstrated. **23rd January 2020** Roche's FIREFISH clinical trial of risdiplam treatment with 21 infants with SMA Type 1 met its primary endpoint. *R*isdiplam demonstrated statistically significant and medically meaningful motor milestone improvement in these infants i.e. the proportion of infants sitting without support for at least five seconds at 12-months of treatment, assessed by the Gross Motor Scale of the Bayley Scales of Infant and Toddler Development Third Edition (BSID-III). Safety for risdiplam in this study was consistent with its known safety profile and no new safety signals were identified. **6th Feb 2020** Roche's global placebo-controlled SUNFISH clinical trial Part 2 (n= 180) evaluating risdiplam in people aged 2-25 years who have SMA Type 2 or 3 showed that the change from baseline in the primary endpoint of the Motor Function Measure 32 scale (MFM-32) was significantly greater in people treated with risdiplam, compared to the placebo. The Revised Upper Limb Module also showed an improvement. **Roche plans to file with the European Medicines Authority in the first half of 2020.** **On 13th January Roche announced its plans for furthering its Global Compassionate Use Access Programme.** The company confirmed it will consider individual compassionate use applications made by UK healthcare professionals on behalf of their patients who have SMA Type 1 and meet the programme's criteria. In the first half of 2020, Roche plans to apply to the Medicines and Healthcare products Regulatory Agency (MHRA) for an Early

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		Access to Medicines Scheme (EAMS) for risdiplam. If accepted, the programme will open to healthcare referrals for those who have SMA Type 2 and meet the programme's criteria. **These developments indicate a NICE appraisal would be highly appropriate at this time.**
Wording	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.*	It does not refer to all the clinical trials that are underway (see above and below). We understand that more than 400 patients have been / are being treated across all the studies. It does not refer to 5q SMA Type 0 at the most severe end of the spectrum.
Timing Issues	*What is the relative urgency of this proposed appraisal to the NHS?*	**Very urgent** – without intervention for breathing difficulties, SMA Type 1 typically causes death before age 2 years. SMA Type 2 is also life threatening. All Types of SMA can be severely disabling, impacting on both patient and family. As outlined in the remit - for this health technology evaluation, nusinersen, the only possible treatment for those who have SMA Type 1, 2 or 3 and meet the eligibility criteria of the Managed Access Agreement, will not be considered as a comparator. There is no routinely commissioned drug treatment for this condition. The SMA community is closely following developments with this treatment and is anxious that the UK is not, as was the case with nusinersen, one of the last countries in Europe to finally approve managed access to the treatment. This followed a long appraisal process which we hope can be avoided this time.
Any additional comments on the draft remit We suggest any appraisal should include a review of any clinical evidence and clinical advice as to whether risdiplam treatment would be appropriate for infants who are considered to have SMA Type 0.		

Comment 2: the draft scope

Section	*Notes*	Your comments
Background	*Consider the accuracy and*	More accurately:

Section	*Notes*	Your comments
information	*completeness of this information.*	Due to severe and complex symptoms, infants with SMA Type 0 rarely survive the first weeks of life. Without intervention for breathing difficulties, SMA Type 1 typically causes death before age 2 years. Care and management **should** follow the guidelines agreed by international experts as documented in the International Standards of Care for SMA (SoC). However, there is no directive from NICE/NHS England to ensure this and, due largely to lack of resources, care and management for many falls short of what is recommended.
The technology/ intervention	*Is the description of the technology or technologies accurate?*	Yes, though not all the trials that are taking place are referenced: **FIREFISH:** SMA Type 1, 21 children aged 1-7 months **SUNFISH:** SMA Types 2 and 3, Part 1: 51 people aged between 2-25 years. Part 2: 180. **JEWELFISH:** targeted 174 people aged 6 months-60 years who have previously participated in a trial with *SMN2*-targeting therapies, or **olesoxime**, or who received previous treatment with **nusinersen** **RAINBOWFISH:** infants with genetically diagnosed SMA who are not yet presenting symptoms (pre-symptomatic); target of 25 children – the first one recruited in August 2019.
Population	*Is the population defined appropriately? Are there groups within this population that should be considered separately?*	This should specify children and adults who have **5q** SMA. This includes those with the currently used clinical classification / diagnosis of SMA Types 1, 2, 3 and 4. There should also be appropriate inclusion / reference (as guided by expert clinicians) to infants who have SMA Type 0. There is no distinct differentiation between types – SMA is a continuum. Age of onset of symptoms guides clinical classification but the impact of the condition varies greatly both between and within these classifications. There is consensus (SoC) that use of the observation that someone is a 'non-sitter' 'sitter' or walker' is a more useful guide for appropriate care and management, though this itself fails to address, for example, the impact of SMA on upper body strength, fatigue, fine motor function and the potentially

Section	*Notes*	Your comments
		devastating impact of loss of any of these abilities It should also clearly include infants with genetically diagnosed 5q SMA who are not yet presenting symptoms (pre-symptomatic) – these infants are being identified for the clinical trial RAINBOWFISH.
Comparators	*Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared? Can this (one of these) be described as 'best alternative care'?*	We agree that the 'Best Supportive Care as outlined in the SoC' is the most appropriate comparator for the reasons given in the remit. We also note that though 'Best Supportive Care as outlined in the SoC' **should be** the best alternative care and is **a requirement** of the nusinersen MAA, this level of care is not available routinely e.g. acute shortage of physiotherapy. Without it, the impact of any treatment is not maximised.
Outcomes	*Will these outcome measures capture the most important health related benefits (and harms) of the technology?*	We agree with all that are listed but suggest some expansion as follows: • Motor function - including **gross and fine** motor function, **upper and lower limb strength** • Complications of SMA (including for example, scoliosis, muscle contractures, **impact on swallowing and ability to communicate**) • Health-related quality of life **for both patient and carer, including mental health and well-being**
Economic analysis	*Comments on aspects such as the appropriate time horizon.*	We note the significant difficulties there were with the economic analysis for nusinersen and that the NICE committee's consultation paper (August 2018) raised concerns that identifying robust utility values in babies and young children is exceptionally challenging. **Appropriate Measurement Tools** Though we are aware that there are considerable efforts underway to develop appropriate tools, we draw attention to the flaws measures can present when applied (not specifically to the paediatric SMA population) - as summarised well 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

Section	*Notes*	Your comments
		115 / ISSUE 5 : • Children undergo dramatic changes in growth and function (e.g., mobility, self-care) at different rates, difficulties may arise with attributing 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 that impact on daily living for both child and parents; measurement tools are insufficiently subtle and limited in their measurements. This last point is confirmed in many studies that show this, for example, Srikrishna S, *et al.* **(**2009*)* **Is there a discrepancy between patient and physician quality of life**

Section	*Notes*	Your comments
		assessment? Neurourol Urodyn. 2009;28(3):179-82. doi: 10.1002/nau.20634. **We are not aware of appropriate robustly validated patient reported outcome measuring tools that focus on treatment outcomes but consider this a vital element in any economic analysis.** It is also essential that any measures are considered in relation to the natural history of the condition. Though there is a growing body of evidence on this, this is not always clear cut due to the variation in impact of 5q SMA. Additionally, with sufficient allocation of resources, there are likely to be ongoing changes and improvements to the base case of best supportive care. The NICE nusinersen committee (August 2018) further concluded that quantifying carer -related disutilities was extremely difficult. **A wider perspective** We are concerned that an economic analysis should cover **all** related health and personal health and social services costs including: • **the costs caused by the impact of the condition on mental health, emotional and psychological well-being – for the patient and carers** • **equipment costs and housing adaptations** • **emergency hospital stays, surgery and clinic time** • **continuing health care (CHC) cost** **Length of time** We accept that, due to the length of time the treatment has been trialled, there will be uncertainty as to future long-term outcomes for those treated with this therapy. However, the evidence to date, when other treatments have been assessed and studies and surveys undertaken, clearly indicates that positive treatment outcomes result in these wider costs potentially reducing significantly. We

Section	*Notes*	Your comments
		consider it vital that this potential is adequately reflected in the ICER. We are also concerned that any model needs to reflect that the health impact is not only on **one** carer but also on the many e.g. grandparents often play a key role. Also, that due to the 'carer burden' of caring for someone with SMA, that impacts on other caring responsibilities of the carer e.g. a parent who is unable to care for a sick or elderly relative such that their care needs fall to health and personal social services. However much effort is made to adjust the ICERs to better reflect evidence and address shortcomings, we suggest that NICE's economic analysis remains fundamentally flawed as it does not reflect the much wider impact in the 'real world' of the costs of the condition and potential benefits of treatment. From our perspective there needs to be a much more holistic approach as only then can the ICERs really begin to reflect the true potential value of this and any treatment. As examples of this 'real world' wider impact of 5q SMA, there are: • **education costs**: requiring Teaching Assistants, school adaptations • **work costs:** in the long-term loss of potential productivity for the adult with SMA and loss of their contribution to the economy through work / taxes; carers (parents and grandparents) who have to give up work to care for their child; partners who give up work • **health and social care costs borne by families:** interventions and support paid for by health and social services and included in NICE's model are insufficient for families to manage and are 'topped up' either formally or informally by the family e.g. care hours • **many equipment and housing**

Section	*Notes*	Your comments
		adaptation costs are borne by families **In summary: we strongly suggest that NICE adopts an economic analysis that includes:** • **all these 'real-world' costs that are currently not included in their model** • **all aspects of the health and personal health and social services required to support anyone who has 5q SMA and their family** • **the impact of SMA affecting more than one carer.**
Equality	*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 proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:* • *could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;* • *could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. 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 tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.*	The proposed remit and scope appears broad enough to ensure that the following points are all carefully considered: It is vital to ensure that all who meet the treatment criteria have equal access, no matter where they live. In view of the fragility of infants with the severest SMA, the risk of respiratory infection and the challenges of travelling for many, access should be local. Ideally, the option of the treatment delivered to the person's home should be available. The impact of SMA on each individual varies. Clinical classification by type is not a reliable predictor of the path an individual's SMA will follow and the impact it will have on their life and the lives of any carers. For example, we support many children who have SMA Type 3 who have lost their ability to walk at an early age and who are very weak and whose day to day lives are not dissimilar to those who are clinically classified as having SMA Type 2. Given this spectrum of 5q SMA and that there are no clear lines between types, we consider **all with the condition should have equal opportunity for access, including those who are pre- symptomatic.** However, we suggest clinical opinion is needed as to whether this should include infants who have the very severest SMA Type 0. The NICE decision re: the nusinersen MAA that excluded so many children and adults

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<tr><th>Section</th><th>Notes</th><th>Your comments</th></tr>
<tr><td></td><td></td><td>with SMA Type 3 has had a devastating emotional and psychological impact on this population who continue to experience the ongoing impact of their condition which causes increasing weakness. We conducted a survey in Jan / Feb 2020 of the impact of the MAA’s exclusion criteria on this group, and their relatives. We had replies from 33 young people and adults (patients) and 22 relatives (replies relating to the 33 and a further 5 patients). The 38 patients (5 ‘proxy’ responses) reported that the decision had impacted them as follows:
<table>
<tr><td></td><td colspan="3">%</td></tr>
<tr><td></td><td>Strongly agree</td><td>Agree</td><td>Total</td></tr>
<tr><td>Made me stressed</td><td>54</td><td>22</td><td>76</td></tr>
<tr><td>Affected me emotionally</td><td>57</td><td>22</td><td>79</td></tr>
<tr><td>Made me anxious</td><td>46</td><td>22</td><td>68</td></tr>
<tr><td>Made me angry</td><td>57</td><td>22</td><td>79</td></tr>
<tr><td>Affected my day to day well-being</td><td>42</td><td>14</td><td>56</td></tr>
</table>

Any decision that will exclude part of the 5q SMA population will have a similar adverse impact. We urge NICE to consider this in their deliberations.

It is also vital that NICE is aware that the SMA population has strongly stated that for them treatment is a success if it achieves the outcome stabilisation of the condition. There were 1,327 validated responses from SMA patients/parents to SMA Europe’s survey conducted in July – August 2019 (not yet published). They were asked, ‘If there was a drug to stabilize your current clinical state, would you consider this progress in your opinion?’ 96.7% replied ‘yes’. This was 97.4% of those not receiving treatment (n=846) and 95.1% of those receiving treatment (n=365).</td></tr>
<tr><td>Other considerations</td><td>Suggestions for additional issues to be covered by the proposed appraisal are welcome.</td><td>It is of great concern that the nusinersen MAA has excluded many people living with SMA from the possibility of treatment – with the devastating consequences as outlined above.</td></tr>
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Section	*Notes*	Your comments
		We are aware that evidence for all treatments is pointing to the earlier it takes place the better the potential outcome. However, there are also positive results in older people and indeed, the longer the duration of treatment the more potential there is for further positive outcomes. The **JEWELFISH** clinical trial: for people aged 6 months-60 years who have previously participated in a trial with *SMN2*-targeting therapies, or **olesoxime**, or who received previous treatment with **nusinersen** has been designed to include all ages and all 'types' of 5q SMA. As argued above, unless this produces clear evidence that the treatment causes a worsening of the condition in a clearly defined sub-group, we strongly suggest that the treatment **should be available to all with 5q SMA** and, recognising 'the earlier the better', should include pre-symptomatic children.
Innovation	*Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* *Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.*	Risdiplam is the first orally-administered liquid designed to provide a sustained increase in SMN protein centrally and peripherally, through daily dosing. As such this is a huge step change for SMA making administration possible for all. It also addresses some of the limitations there may be with any treatments that are unable to cross the blood brain barrier. Roche has been engaged in surveys and studies of the economic and health related impact of SMA. They have consulted with the SMA Patient community over the structure of these studies and the PAGs have assisted with their dissemination. As such we consider they will be able to present important data. NICE has also gathered a significant amount of data via the appraisal of nusinersen. Though we are aware each appraisal is separate we would hope that relevant aspect of this data (gathered and submitted by patients, clinicians, pharma company) can be referenced.
Questions for consultation	*Please answer any of the questions for consultation if not covered in the above sections. If appropriate, please include comments on the proposed process this appraisal will follow (please note any changes*	**Do you consider that there will be any barriers to adoption of this technology into practice?** We cannot see there being any barrier

Section	*Notes*	Your comments
	made to the process are likely to result in changes to the planned time lines).	caused by the method of administration. We imagine clinicians caring for patients who do not have access to nusinersen will welcome this treatment as will the patients themselves. One barrier may be the lack of reliable comparative information about the efficacy of the various possible treatments. This would make it difficult for a patient / carer faced with more than one option to make a choice. The best possible comparative information will need to be developed as quickly as possible to assist patients and clinicians. As always, price could be a barrier if this treatment is appraised via an STA route designed for common conditions - with its low-cost effectiveness threshold. **Suitability of a Single Technology Appraisal Process** There is still a binary choice of an STA versus an HST route. The higher cost effectiveness threshold of the HST would be more appropriate for what is a rare condition. However, this is a treatment that is potentially suitable for all with 5q SMA therefore it does not meet the extremely rigid and low HST barrier in terms of population numbers. Similarly, as access to treatment will not need to be via a very small number of treatment centres, this criterion will not be met. In view of this and that nusinersen was appraised via an STA route, the choice has to be an STA process. However, we urge the NICE committee when it meets to be as flexible as possible in its appraisal. We continue to hope that we will soon see a change to this rigid binary system.
Any additional comments on the draft scope		

Comment 3: provisional stakeholder list of consultees and commentators

The provisional stakeholder list of consultees and commentators (Appendix C) is a list of organisations that we have identified as being appropriate to participate in this proposed appraisal. If you have any comments on this list, please submit them in the box below.

As NICE is committed to promoting equality and eliminating unlawful discrimination Please let us know if we have missed any important organisations from the lists contained within the

stakeholder list, and which organisations we should include that have a particular focus on relevant equality issues.

If you do not have any comments to make on the provisional stakeholder list of consultees and commentators, please cross this box: ☐

Comments on the provisional stakeholder list of consultees and commentators

Comment 4: regulatory issues (to be completed by the company that markets the technology)

Section	*Notes*	Your comments
Remit	*Does the wording of the remit reflect the current or proposed marketing authorisation? If not, please suggest alternative wording.*	
Current or proposed marketing authorisation	*What are the current indications for the technology?*	
	What are the planned indications for the technology?	
	FOR EACH PLANNED INDICATION:	
	Which regulatory process are you following?	
	What is the target date (mm/yyyy) for regulatory submission?	
	What is the anticipated date (mm/yyyy) of CHMP positive opinion (if applicable)	
	What is the anticipated date (mm/yyyy) of regulatory approval?	
	What is the anticipated date (mm/yyyy) of UK launch?	
	Please indicate whether the information you provide concerning the proposed marketing authorisation is in the public domain and if not when it can be released. All commercial in confidence information must be highlighted and underlined.	

Section	*Notes*	Your comments
Economic model software	*NICE accepts executable economic models using standard software, that is, Excel , DATA, R or WinBUGs. Please indicate which software will be used. If you plan to submit a model in a non-standard package, NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non –standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software*	

Please complete this form and upload it to NICE Docs by **Monday 24 February 2020**.