NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Nusinersen and risdiplam for treating spinal muscular atrophy (review of TA588 and TA755) ID6195

Stakeholder comment form

Please use this form for submitting your comments on the draft remit, draft scope and provisional list of stakeholders. 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 and Muscular Dystrophy UK

Comments on the draft remit and draft scope

The draft remit is the brief for an evaluation. Appendix B contains the draft remit. The draft scope, developed from the draft remit outlines the question that the evaluation 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 evaluation, 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 **Friday 25 August 2023.** If using NICE docs is not possible, please return via email to scopingta@nice.org.uk If you have any questions please contact Emily Richards, Project Manager on (0)161 413 4070 or at the above email address.

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 and proposed evaluation route

Section	*Notes*	**Your comments**
Appropriateness of an evaluation and proposed evaluation route	*NICE welcomes comments on the appropriateness of evaluating this topic and the evaluation route proposed (single technology appraisal, multiple*	While we have welcomed assurances from NICE that the MTA process is not designed as a 'competition' between the two treatments, we remain concerned that by comparing the two treatments to each other as well as to best supportive care, this comparison may influence the final committee

Section	*Notes*	Your comments
	technology appraisal or highly specialised technology evaluation).	decision. It is likely, and we have seen in many real world cases, that some patients will better tolerate one treatment over another even if clinical data suggests a treatment may have better outcomes for them, and so a choice of treatments available to them and their clinicians is essential. We are also concerned that there will be more data available regarding Nusinersen as the MAA for this treatment has been running for longer, and would welcome assurances that this will be taken into account. It is vital that the appraisal does not have the aim to recommend just one treatment. Given the range of experiences across both treatments it is also essential that the number of clinical and patient experts involved reflects this and that experience of both treatments is equally represented.
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.***	Yes
Timing Issues	*What is the relative urgency of this evaluation to the NHS?*	Very urgent. There is currently only one out of the three novel disease modifying treatments for SMA available on the NHS, Zolgensma gene therapy. Access to an assessment for this treatment is limited to young children diagnosed with type 1 SMA who are 12 months old or younger and have 1- 3 copies of the SMN2 gene. Access for children up to 21kg (as stipulated by EMA guidelines) can be discussed on a case by case basis by a National Multidisciplinary Team (NMDT) of expert clinicians. With concerns that heavier children may have increased risks of adverse side effects, the NMDT examine the risks and benefits of each case carefully. There are no treatments routinely available on the NHS for those people living with SMA

Section	*Notes*	Your comments
		who are not eligible for Zolgensma. For children and adults living with SMA, from type 1 to type 3, who are receiving risdiplam or nusinersen on the MAA, routine commissioning will alleviate anxieties that their disease modifying treatment may not be available to them long term. Withdrawal of any of these treatments would be catastrophic for children and families, with a significant negative impact on quality of life, increased care requirements and potential loss of life for the more severely affected.
None		

Comment 2: the draft scope

Section	*Notes*	Your comments
Background information	*Consider the accuracy and completeness of this information.*	SMA types are a broad clinical classification, SMA is a disease spectrum. How severely children, young people and adults are affected, both within and between 'Types' can vary greatly as you can see in this infographic [1] We suggest explaining this with this wording in paragraph 3 of the background information: **Having more *SMN2* copies is generally associated with less severe SMA symptoms. However, at an individual level, accurate predictions cannot be made about the Type or severity of SMA based on the *SMN2* copy number alone.[2] [3]**

[1] David Christof Schorling **et al** (2019) Advances in Treatment of Spinal Muscular Atrophy – New Phenotypes, New Challenges, New Implications for Care Journal of Neuromuscular Diseases

[2] A Guide to the 2017 International Standards of Care for SMA. Available at: smauk.org.uk/international-standards-of-care-for-sma (Last accessed: 25th July 2022).

[3] Mercuri E et al. (2018) Diagnosis and management of spinal muscular atrophy: Part 1: recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscul Disord 28*: 103-115.

Section	*Notes*	Your comments
		When portraying type 3 SMA at the end of the 2nd paragraph, you say*:* *'most people with type 3 SMA can walk or sit unaided at some point, but many lose mobility over time1*' Adding: '**The earlier the onset of symptoms the more likely they will lose their ability to walk and be wheelchair users**.' would add clarity. Within the type 3 spectrum, unfortunately **90% of SMA 3A kids lose ability to walk before adult life**, and also many 3b patients suffer progressive weakness[4] [5] (as seen in this chart), so while it is a "milder" disease compared to the other variants, it is a very serious disease, we would not want the information to diminish the severity of this form of the condition. The information states '. *Currently in England only a small number* of people are identified pre-symptomatically.' To highlight just how rare this is in the UK without newborn screening, it is worth adding ' **only in cases where a sibling has been diagnosed with SMA'** The 4th paragraph of the background information begins, *'SMA affects an estimated 1 in 10,000 births worldwide,[3] and the incidence varies between different types of SMA.'* For a more comprehensive and up to date understanding of the incidence variation, including the higher prevalence of the more severe type 1 SMA, and the prevalence of the faulty gene within the general population it could read:

[4] **Catherine L Bladen** et al (2014) Mapping the differences in care for 5,000 spinal muscular atrophy patients, a survey of 24 national registries in North America, Australasia and Europe **Epub 2013 Oct 27.**

[5] Giorgia Coratti et al (2020) Clinical Variability in Spinal Muscular Atrophy Type III Epub 2020 Oct 2.

Section	*Notes*	Your comments
		Approximately 1 in 40 people carry the faulty SMN1 gene[6] – that means there are around 1.67 million carriers in the UK.. Studies published in 2017 indicate that approximately one in every 10,000 babies worldwide are born with a Type of SMA, and that SMA Type 1 accounts for approximately 60% of cases[27]. Please see https://smauk.org.uk/support-information/about-sma/what-is-5q-sma/ For the most up to date incidence and prevalence data. In the final paragraph, you mention the international stantards of care. '*Treatment usually follows guidelines from the International Standards of Care Committee for Spinal Muscular Atrophy*[4,5]. For transparency, we suggest adding: **However, this guidance was written when only nusinersen was on the horizon and before all three treatments became more widely available. There is ongoing work to review and update these SoC which must go hand in hand with treatments.** **<u>The Technologies</u>** You say: *'Nusinersen has a marketing authorisation in the UK for treating 5q SMA'* In your description of the Risdiplam marketing authorisation, you include further details on eligible groups: ' *for the treatment of 5q SMA in patients 2 months of age and older, with a clinical*

[6] Verhaart IEC et al. (2017) Prevalence, incidence and carrier frequency of 5q–linked spinal muscular atrophy – a literature review. *Orphanet J Rare Dis 12*: 124

[7] Verhaart IEC, et al. (2017) A multi-source approach to determine SMA incidence and research ready population. *J Neurol 264*: 1465-1473.

Section	*Notes*	Your comments
		diagnosis of SMA type 1, type 2 or type 3 or those with one to four SMN2 copies.' We suggest the descriptors for both drugs should be the same and refer to both the marketing authorisation and what is possible under the current MAAs as these may well be different. In terms of the MAAS, nusinersen and risdiplam are available for treatment of SMA types 1, 2 and 3 and pre-symptomatically identified babies with 1 – 4 SMN2 copies. Risdiplam is only from 2 months onward, given new data from the Rainbowfish trial, and the upcoming recommendation from the UKNSC, the SMA community would welcome access to risdiplam from birth.
Population	*Is the population defined appropriately?*	The SMA community welcome that the population is defined as **all** with 5q SMA as this includes discussion of the potential eligibility for those living with 5q SMA with the clinical diagnosis SMA type 4 and type 0.
Subgroups	*Are there groups within the population that should be considered separately? For example, are there subgroups in which the technology is expected to be more clinically or cost effective? If subgroups have been suggested in the scope, are these appropriate?*	The range of potential subgroups seems appropriate so that there is a full discussion as to which ones will continue to have meaning. Though a clinical diagnosis is still given, this classification for SMA was established prior to the availability of genetic testing and prior to the availability of disease modifying treatments. Now that it is possible to identify the number of SMN2 copies, this is a more useful indicator of the likely development of the condition without treatment. It is important to note however, that there are still variations within populations with the same number of SMN2 copies, so functional milestones, as well as the impact of the condition on breathing, swallowing and mobility should be looked at alongside copy numbers.

Section	*Notes*	Your comments
Th	*Are the comparators listed considered to be the standard treatments currently used in the NHS with which the technology should be compared? Have all relevant comparators been included?*	There is significant concern within the SMA community that the two treatments are being compared with each other. Nusinersen uses more NHS time, expertise, and spaces - and though we understand this is taken into account in the economic models, there are concerns that in view of the overall pressures on the NHS this could be seen as a disadvantage of this treatment. Neither one of these treatments can meet the needs of the SMA population alone, it is important that this fact is clear when comparing the two drugs with each other. Some adults who have experienced adverse side effects with one have switched to the other. It is crucial that this carefully managed flexible approach remains an option in order to get the best outcomes for individuals across the spectrum of SMA.
Outcomes	*Are the outcomes listed appropriate? Will these outcome measures capture the most important health related benefits (and harms) of the technology?*	For adults living with SMA, the treatments do not have the significant transformative effect that they have on children, due to irreversible muscular atrophy. It is, however, important to recognise the value of stabilisation within this population. Not losing the ability to drive a power chair or to chew and swallow food for example, are important and highly valued benefits. Quality of life and independence would be seriously compromised resulting in additional health and social care measures being put in place if access to these treatments was prohibited. It was anticipated that the real world data from the collection of PROMs would be able to fill the gaps seen in clinical data. Many families living with SMA do not see their young children achieve on tasks in the clinic environment that they know they achieve home. Many adults feel the clinic assessments do not capture the difference stability and subtle gains make to their day to day lives. We are aware that the collection of PROMS has been a challenge and there is not the volume of data aligned with the clinical data to make a significant impact. However, this

Section	*Notes*	Your comments
		does not mean that real world evidence should not be highly valued.
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 draft remit and scope may need changing in order to meet these aims. In particular, please tell us if the draft 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.*	It would be important to ensure that all people meeting the treatment criteria have equal access to treatment, no matter where they live. We also suggest that consideration of access by all who have 5qSMA, perhaps within a specified SMN2 copy range and considering other aspects of health when a baby is assessed at birth, is essential for an equitable service. A recommendation to routinely commission one treatment but not the other would make equitable access impossible. Some people living with SMA cannot access Nusinersen due to, for example, complications of scoliosis and others cannot tolerate Risdiplam because of adverse side effects such as gastric problems. The only way to ensure equitable access for the whole community is with routine commissioning of both treatments.
Other considerations	*Suggestions for additional issues to be covered by the evaluation are welcome.*	
Questions for consultation	*Please answer any of the questions for consultation if not covered in the above sections.*	**What treatments would be considered to be established clinical practice in the NHS for treating people with spinal muscular atrophy if nusinersen and risdiplam were**

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		not currently available through a managed access agreement? Zolgensma is the only disease modifying treatment that would be available, with access limited to young children diagnosed with type 1 SMA who fulfil the eligibility criteria. The only other treatment is best supportive care as stipulated in the Standards of Care for SMA 2017[8]. A 2022 study showed that ' access (to the recommended standards of care in the UK) is not equal for adults and children and access to certain professionals is significantly limited.' [9] Best supportive care is not equitable across the UK and does not halt the progression of the disease. **What are the reasons children otherwise eligible for onasemnogene abeparvovec instead have treatment with nusinersen or risdiplam?** • Parental choice, particularly with heavier children and those with more complex needs. • Case specific clinical judgement where risk is considered to outweigh the benefits. **Do you consider that the use of nusinersen or risdiplam can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculations?**

8 *Eugenio Mercuri et al (2018) Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care Neuromuscular Disorders* Volume 28, Issue 2, February 2018, Pages 103-115

Richard S. Finkel et al (2018) Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics Neuromuscular Disorders Volume 28, Issue 3, March 2018, Pages 197-207

9 Robert Muni-Lofra et al (2022) Real-World Data on Access to Standards of Care for People With Spinal Muscular Atrophy in the UK

Section	*Notes*	Your comments
		We understand that all direct health and personal health and social services costs including to social services, should already be included in QALY calculations: • mental health: • equipment costs and housing adaptations: • emergency hospital stays, surgery and clinic time: • continuing health care (CHC) cost. We draw attention to the need to include in QALY calculations: • **health and social care costs borne by families and individuals:** interventions and support paid for by health and social services and included in NICE's model are insufficient for families and adults living with SMA to manage and are 'topped up' either formally or informally by the family e.g. care hours. Many equipment and housing adaptation costs are borne by families or individual adults living with SMA. We are aware that both pharmaceutical companies have undertaken substantial work to better understand **'the carer burden'** and incorporate what they have learned in their models. We have been involved in some of these conversations. Importantly, the carer burden aspect of the QALY should reflect: • The number of informal carers that are impacted. We remain concerned that the QALY calculations may still not capture all costs, often due to the limitations of using 'health-related costs and benefits' in the models. We therefore continue to draw attention to the key real-world costs that may still be excluded but are an outcome of SMA, that reduce with treatment: • **Education/ workplace costs**: Teaching Assistants, school adaptations. Access to work adaptations / PA support

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		• **Work costs:** informal carers who have to give up work to care for the person living with SMA, and in the long term loss of potential productivity and contribution to the economy through work / taxes. We are also concerned that the development of PROMS measures and the collection of this data hasn't been progressed as much as we hoped and we have concerns that this may not have sufficient recognition in the QALY calculations **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** We have alerted the pharma companies to all the above points and asked for them to be taken into account in any modelling. Real world experiences have been captured through the PROMs project, led by the REACH clinical network. Data from the PROMs should begin to fill the data gaps, this will include the adult's perspective where very small gains or stabilisation has a highly positive effect on quality of life. Assessing babies and young children formally within a clinic environment is a stressful situation that rarely reflects their true abilities or progression with real life tasks. The PROMs data shows true and meaningful outcomes from the family's perspective.
Any additional comments on the draft scope		

Comment 3: provisional stakeholder list

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

NICE is committed to promoting equality and eliminating unlawful discrimination. Please let us know if we have missed any important organisations from the 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 Stakeholders missing from the list: **Patient/ Carer groups:** ACE SMA https://acesma.co.uk/ Pathfinders neuromuscular alliance https://www.pathfindersalliance.org.uk/ **Healthcare professional groups:** Paediatric SMA Reach https://smareachuk.org/

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?	

Section	*Notes*	Your comments
	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 EU regulatory approval?	
	What is the anticipated date (mm/yyyy) of UK regulatory approval if different to Europe?	
	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.	
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 EAG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the EAG with temporary licences for the non – standard software for the duration of the evaluation. NICE reserves the right to*	

Section	*Notes*	Your comments
	reject economic models in non-standard software	

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