National Institute for Health and Care Excellence

Health Technology Evaluation

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

Response to stakeholder organisation comments on the draft remit and draft scope

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 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Roche Products Ltd.	Whilst Roche understands the ambition of simplifying and enabling consistency of decision making, Roche do not consider an MTA to be an appropriate route of post managed access evaluation for risdiplam for the following reasons: ● An MTA in a disease area such as SMA may lead to significant risks and complications in conducting a fair appraisal of each technology. In later-onset SMA, this is mainly due to the differences between the nusinersen (CHERISH) and risdiplam (SUNFISH) patient populations as a result of trial eligibility criteria. CHERISH subjects were excluded for a baseline Hammersmith Functional Motor Scale (HFMSE) score <10, severe contractures or scoliosis at screening, ventilation for >6 hours or having a nasogastric tube fitted. In comparison, for SUNFISH there were no exclusion criteria related to the degree of scoliosis, contractures, feeding support or non-invasive ventilation. Moreover, the oldest subject recruited in CHERISH was 9 years of age, whereas the oldest subject in SUNFISH was 25 years old. A table of key	Thank you for your comment. We have determined that MTA remains the appropriate route for this evaluation based on extensive discussions during the period of managed access. Reasons include: 1. Concurrent timing of MAA

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baseline demographics and clinical characteristics for CHERISH (taken from TA588) and SUNFISH (taken from TA755) are below (2,3):
<table>
<tr><th></th><th>Age at screening (years), median (range)</th><th>Age at symptom onset (months), median (range)</th><th>HFMSE scores, mean (SD)</th><th>RULM scores, mean (SD)</th><th>Severe scoliosis (>40° Cobb angle), n (%)</th></tr>
<tr><td>CHERISH (nusinersen treatment group)</td><td>4 (2-9)</td><td>10.00 (6-20)</td><td>22.40 (8.3)</td><td>19.40 (6.2)*</td><td>0</td></tr>
<tr><td>SUNFISH (risdiplam treatment group)</td><td>9 (2-25)</td><td>12.30 (0-57)</td><td>16.10 (12.46)</td><td>19.65 (7.22)</td><td>34 (28%)</td></tr>
<tr><td colspan="6">*the figure is reported as 19.5 within the nusinersen company evidence submission, but the reference Mercuri (2018) reports this as 19.4 (1).
Figures taken from TA588 (2) and TA755 (3)</td></tr>
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Evidently the baseline characteristics of subjects involved in the two trials is significantly different, where the CHERISH trial includes a younger population with less severe disease progression, versus the SUNFISH baseline characteristics.

In addition, due to significant differences in the study populations (age, baseline HFMSE score, presence of scoliosis and severe contractures) and different clinical trial endpoints (CHERISH primary endpoint: HFMSE; SUNFISH total Motor Function Measure-32 (MFM-

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exit for both technologies
2. Both technologies cover the same indication
3. Allows committee to assess data for both technologies at the same time

On your concerns about delays to both technologies, guidance for a single technology evaluated in an MTA can be published if the committee were able to do so, even if another topic is delayed, though this detail is not needed in the scope.
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		32)), the indirect treatment comparison between risdiplam and nusinersen is associated with vast uncertainties. ● The differences in baseline characteristics of treated patients is similarly reflected in the real-world use of these two technologies in the UK during managed access. Therefore the risdiplam and nusinersen registry data should not be compared for the following reasons: ○ Due to the timing of the managed access agreements, the SMA patient population had the opportunity to receive nusinersen before risdiplam was available. As such, only patients ineligible to receive nusinersen via intrathecal injection, i.e. due to scoliosis or contractures (a good marker of disease progression), received risdiplam once it became available. ○ Patients have not been switching freely between products during the managed access period which has sustained the population differences. The combination of these two factors has unknowingly created a biased population. Trying to compare these groups risks creating more uncertainty versus what could be achieved if each evidence base was considered separately. ● The MTA route has no ability to separate the appraisals in the event that challenges arise in one or the other. Under the MTA, there is a risk where uncertainties associated with one technology have been resolved during the MAA period but further data and/or discussion is required for a committee decision on the second technology, and as a result both technologies are delayed access as the guidance for each hinges on completion of the entire appraisal for both technologies. The delay would impact NHSE, clinical sites, patients and caregivers	

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		as the administrative burden to accessing these treatments continues until routine commissioning is in place.	
	Biogen Idec Ltd	Biogen agree that a multiple technology appraisal is an appropriate route for evaluating nusinersen and risdiplam given both of these technologies are due to exit their respective managed access agreements (MAA) at similar times and are both indicated for the treatment of 5q spinal muscular atrophy. Furthermore, Biogen request NICE make all efforts to use the highly specialised technology (HST) appraisal committee (the same committee as used in the original appraisals of nusinersen and risdiplam) for this upcoming appraisal. Whilst nusinersen for the treatment 5q spinal muscular atrophy was previously considered not to meet the criteria for an HST appraisal due to its epidemiology, it does share many characteristics of ultra-rare diseases that require specific considerations and flexibilities to handle uncertainty due to a small number of patients, limited treatment options and challenges in research/ collection of evidence due to the nature of this heterogenous disease which significantly shortens life and severely impairs quality of life.	Thank you for your comment. The scheduling team will take into account these factors and allocate an appraisal committee according to the needs of the appraisal.
	Novartis Gene Therapies, Inc.	Novartis Gene Therapies agree that both the timing and proposed evaluation route are appropriate, given that the managed access agreement (MAA) for risdiplam is nearing its completion date (March 2024) and data on nusinersen has been collected for the necessary time period (at least 3 years). Thus, at this stage a NICE guidance is needed to outline routinely commissioned treatment options in the identified patient population with 5q spinal muscular atrophy (SMA) based on the collected data on nusinersen and risdiplam.	Thank you for your comment.
	Spinal Muscular Atrophy UK and Muscular Dystrophy UK	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 decision. It is likely, and we have seen in many real world cases, that some	Thank you for your comment. We can echo the earlier assurances that both technologies will be evaluated within

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		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.	the MTA and the process is not designed to result in only one recommendation for routine use in the NHS. The committee will recommend all options that it considers a clinically- and cost-effective use of NHS resources.
	TreatSMA	Appropriate	Thank you for your comment.
	Association of British Neurologists – Neuromuscular Advisory Group	NICE intends to appraise this technology through its Multiple Technology Appraisal (MTA) process – this is appropriate given incidence of SMA and numbers of people eligible in England.	Thank you for your comment.
	Newcastle EAG	The EAG note that the managed access agreements for the two technologies in scope of the review differ (by 30 months). This may impact the availability of data (including longitudinal outcomes) and the comparison of such in a multiple technology appraisal. Furthermore, clinical experts consulted during the review of the statistical analysis plans highlighted differences in the populations taking each of the interventions, for example, Risdiplam has a higher proportion of SMA Types II	Thank you for your comment. We have determined that MTA remains the appropriate route for this evaluation based on extensive discussions during the period of managed

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		and III because of differences in eligibility, therefore it may not be appropriate to compare them within a multiple technology appraisal.	access. Reasons include: 1. Concurrent timing of MAA exit for both technologies 2. Both technologies cover the same indication 3. Allows committee to assess data for both technologies at the same time
Wording	Roche Products Ltd.	The remit reflects the issues of clinical and cost-effectiveness for risdiplam, however, for the reasons stated above, we do not agree that risdiplam and nusinersen should be evaluated together within an MTA.	Thank you for your comment.
	Biogen Idec Ltd	Biogen request the addition of '5q' spinal muscular atrophy to reflect the marketing authorisation of nusinersen. As such, we suggest the following wording for the remit: "To appraise the clinical and cost effectiveness of nusinersen and risdiplam within their marketing authorisations for treating 5q spinal muscular atrophy."	Thank you for your comment. The sentence has been amended accordingly.

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	Novartis Gene Therapies, Inc.	Novartis Gene Therapies agree that the wording of the draft remit reflects the clinical and cost-effectiveness issues for the appraisal of nusinersen and risdiplam in the identified population.	Thank you for your comment.
	Spinal Muscular Atrophy UK and Muscular Dystrophy UK	Yes	Thank you for your comment.
	TreatSMA	It does	Thank you for your comment.
	Association of British Neurologists – Neuromuscular Advisory Group	Remit objective is to appraise the clinical and cost effectiveness of nusinersen and risdiplam within their marketing authorisations for treating spinal muscular atrophy – this is reasonable. See comment below regarding inclusion of the different SMA sub-types.	Thank you for your comment.
	Newcastle EAG	Clarification: Intervention is a monotherapy and would be in addition to existing clinical services (same physiotherapy regime etc.)	Thank you for your comment. This has been noted in the PICO table in the scope.
Timing issues	Roche Products Ltd.	There is a high urgency to evaluate these treatments as achieving routine and sustainable access for SMA patients sooner will provide the clinical and patient community with confidence, and reduce the period of uncertainty associated with interim access. In addition, routine commissioning of these treatments would decrease the administrative burden of the managed access data collection agreement on	Thank you for your comment.

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		NHSE, SMA REACH and, particularly, the clinical sites, patients and caregivers.	
	Biogen Idec Ltd	Patients are currently receiving nusinersen under the terms of the MAA which is due to come to an end by 24th July 2025. Therefore, updated NICE guidance prior to this date is essential to ensure eligible patients can continue to access the medicines they need	Thank you for your comment.
	Novartis Gene Therapies, Inc.	Novartis Gene Therapies are aware that the two MAAs specified under the single technology appraisals (STAs) for nusinersen and risdiplam are either approaching their completion (risdiplam) or have been collecting data for the minimum required time (nusinersen). Therefore, Novartis Gene Therapies agree the timing is appropriate to develop a guidance outlining routinely commissioned treatment options in the identified patient population with 5q SMA.	Thank you for your comment.
	Genetic Alliance UK	SMA is a rare condition that can have a significant impact on quality of life. As these technologies have been routed through a MTA it's important that their appraisals are not disadvantaged by the evidence constraints of smaller population numbers.	Thank you for your comment.
	Spinal Muscular Atrophy UK and Muscular Dystrophy UK	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.	Thank you for your comment.

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		There are no treatments routinely available on the NHS for those people living with SMA 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.	
	TreatSMA	Unless MAAs are extended beyond agreed period, this project is urgent	Thank you for your comment.
	Association of British Neurologists – Neuromuscular Advisory Group	Urgent. These treatments are time dependant and early treatment in the course of the disease appears to give better outcomes. This is of clinical benefit and also allows better functional status and reduces health and social care cost. It is important that, for those already receiving treatment via the MAAs, there is no gap in ongoing treatment whilst this review process occurs.	Thank you for your comment.
	Newcastle EAG	As highlighted, there is a paucity of active treatments routinely commissioned for most people with SMA, however the readiness and availability of longitudinal evidence following the availability of the treatments through the managed access agreements may not yet be available to permit meaningful evaluation. Any additional comments on the draft remit Missing word on page 1: “type 3 SMA experience varying degrees OF symptom severity”. Need consistency in writing of (SMN)-2 gene and SMN2 gene.	Thank you for your comment. The scope has been amended accordingly.

Section	Stakeholder	Comments [sic]	Action

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Roche Products Ltd.	1) In the statement “The number of SMN2 gene copies, which encodes the SMN protein that can partially compensate for the loss of the SMN1 gene, is inversely related to the severity of SMA and can be used to predict the course of the disease”. I would suggest changing the wording to “...broadly predict the course of the disease” with a more relevant reference such as Calucho, et al. 2018 (4). 2) For the statement “Currently in England only a small number of people are identified pre-symptomatically”. We would expect this number to increase significantly in coming years if newborn screening for SMA is implemented, this is worth noting. 3) The UK epidemiology numbers are now outdated and use an incorrect link. SMA UK’s new estimate is 1,340 (5). 4) In the description of how risdiplam works it mentions that SMN levels are increased in the CNS and throughout the body, it would be appropriate to call out the fact that nusinersen increases SMN levels in the CNS only.	Thank you for your comments. 1. We accept this suggestion and have incorporated it into the scope 2. We have indicated screening may change incidence in future 3. We note the updated figures and have updated the scope

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			4. We note this additional detail
	Biogen Idec Ltd	Background page 1, para 2: Suggest including a statement pertaining to type 0 and type 4 for completeness. Background page 2, para 1: An additional statement should be included to a highlight the disparity in NICE guidance and NHSE commissioning for onasemnogene abeparvovec for type 1 SMA: Suggested text: *"Children with type 1 SMA who are over 12 months old and within the scope of the drug's European Medicines Agency marketing authorisation may be assessed for treatment if considered appropriate. This is via the NHS England March 2021 agreement."* Background page 2, para 3: Suggest NICE clarify what proportion of the SMA population is currently covered by routinely commissioned treatments and secondly improve accuracy to state there are no active treatment for SMA routinely commissioned "*for type 2 and 3 patients*" The technologies, page 2, para 1 and 2: Request to add further details on treatment posology and evidence base supporting marketing authorisation for nusinersen: Suggested text: "*Nusinersen (Spinraza, Biogen) is a 2'-O-methoxyethyl antisense oligonucleotide which stimulates the survival motor neuron (SMN)-*	Thank you for your comments. We have included suggestions that are informative for the scope and provide more detail. Elsewhere the scope states that 60% of people born with SMA are type 1 and are therefore covered by onasemnogene abeparvovec. The scope now states that there are no active treatments for types 2 and 3. Details on posology provided by you have been added to the technologies section. We have not included NHSE's position on commissioning onasemnogene abeparvovec since it is out of NICE's remit and

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		2 gene to increase SMN protein levels. It is administered via intrathecal injection as 4 loading doses on Days 0, 14, 28 and 63, followed by maintenance dosing every 4 months thereafter for life. *Nusinersen has a marketing authorisation in the UK for treating pre-symptomatic and symptomatic 5q SMA. It has been studied in clinical trials compared with placebo (sham procedure) in infants and children with SMA. There is also an extensive body of real-world evidence studying the effectiveness and safety of nusinersen in 5q SMA across all age-groups[1-3].* The technologies, page 2, para 1 and 2: Request to add further details on treatment posology and evidence base supporting marketing authorisation for risdiplam: Suggested text: *"Risdiplam (Evrysdi, Roche Products) is a small-molecule survival motor neuron-2 (SMN2) gene splicing modifier which increases SMN protein levels in the central nervous system and throughout the body. It is administered orally once daily for life with the dose of determined by age and body weight.* *Risdiplam has a marketing authorisation in the UK for the treatment of 5q SMA in patients 2 months of age and older, with a clinical diagnosis of SMA type 1, type 2 or type 3 or those with one to four SMN2 copies. It has been studied in clinical trials through single-arm studies in infants and compared with placebo in children and adults (aged 2-25 years of age) with SMA."*	provides recommendations based on the available evidence. The committee can consider whether the drug is being used for people over 12 months in their decision making based on expert elicitation.
	Novartis Gene Therapies, Inc.	Novartis Gene Therapies agree the information provided in the draft remit accurately describes the disease and the management of patients with 5q SMA.	Thank you for your comment.

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	Spinal Muscular Atrophy UK and Muscular Dystrophy UK	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]** 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	Thank you for your comment. The background section is intended to be a brief overview of the condition. Thank you for the updated figures on patient numbers, these have been incorporated into the scope. We have noted that the international standards of care are being updated.

[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	Consultee/ Commentator	Comments [sic]	Action
		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: **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**	

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.

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

Section	Consultee/ Commentator	Comments [sic]	Action
		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'*	

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

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		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 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.	
	TreatSMA	Most of the background is correct. It is preferred to move away from Type 1, 2 etc terminology to ability to sit, walk etc. If terminology Type 1, 2 etc… must be used then it has to be subdivided into subtypes. Eg Type 1A, 1B and 1C. etc. More importantly, we must appreciate that there is no clear cut off between the types as SMA is a continuous spectrum. Often a clinician makes a diagnosis of a specific type based on appearance during the diagnosis day. Another clinician may diagnose the same patient differently on another day. Therefore by setting a hard cut offs based on type we risk exclusion of eligible patients.	Thank you for your comment. We note that there is debate in the community about this categorisation and will acknowledge such in the scope.
	Association of British Neurologists – Neuromuscular Advisory Group	Yes accurate	Thank you for your comment.

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Population	Roche Products Ltd.	The current MAA includes patients with spinal muscular atrophy (SMA) in people 2 months and over, with a clinical diagnosis of SMA types 1, 2 or 3 or with pre-symptomatic SMA and one to four SMN2 copies However, for clarity, the anticipated wording of our marketing authorisation is set to broaden to [redacted]	Thank you for providing updated information on the marketing authorisation.
	Biogen Idec Ltd	The population is reflective of the marketing authorisation for both nusinersen and risdiplam However, Biogen request SMA type is moved from subgroups into the population to promote consistency in manufacturer submissions, alignment with the clinical trial evidence base which is delineated by type [4-6] and prior NICE decision making e.g. HST 15 and HST 24 for onasemnogene abeparvovec [7, 8].	Thank you for your comment. SMA types have been moved to the population box to make it clear that types are not subgroups.
	Novartis Gene Therapies, Inc.	Novartis Gene Therapies agree that the population is appropriately defined in the multiple technology appraisal (MTA) draft scope.	Thank you for your comment.
	Spinal Muscular Atrophy UK and Muscular Dystrophy UK	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	Thank you for your comment.
	TreatSMA	Yes - subject to the above considerations	Thank you for your comment.

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	Association of British Neurologists – Neuromuscular Advisory Group	Yes correct	Thank you for your comment.
	Newcastle EAG	The population is clear, however there are stipulations within the managed access agreements for accessing nusinersen or risdiplam: • confirmed Type I, II, III SMA, or pre-symptomatic SMA confirmed with genetic testing with 1 to 4 SMN2 copies. • Nusinersen or Risdiplam used as a monotherapy. • No successful treatment with onasemnogene abeparvovec. • No permanent ventilation or tracheostomy requirement at baseline. Should the Scope align more specifically to these requirements? The EAG note that onasemnogene abeparvovec is indicated for pre-symptomatic or symptomatic Type I patients and is therefore not expected to be used in the adult population.	Thank you for your comment. We have updated the population to include the people with SMA types 0 to 4 and people with pre-symptomatic SMA with 1 to 4 SMN2 copy numbers. Nusinersen or risdiplam used as monotherapy is now included in the intervention box. The latter 2 bullets are conditions of the MAA and not the marketing authorisation, which the scope aligns to.
Subgroups	Roche Products Ltd.	There were no predefined subgroups in FIREFISH (Type 1 SMA).	Thank you for your comment. Clinical experts have identified important subgroups but NICE understands

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		Whilst there were predetermined age subgroups in SUNFISH (Type 2/3 SMA), the trial was not powered to demonstrate a statistically significant difference for these subgroups. Roche does not consider it appropriate to explicitly consider cost-effectiveness in subgroups of patients from our studies, since: ● subgroup analyses would be associated with small patient numbers, increased uncertainty and lack of robustness in any conclusions ● There is a significant remaining unmet need across all types of patients with SMA There may be overlap in terms of disease severity between SMA subgroups, making subgroup comparisons not entirely appropriate.	that data limitations may mean conclusions cannot be drawn for some analyses.
	Biogen Idec Ltd	Aligned with the population comment above, Biogen believe SMA type is better suited there as opposed to a pre-specified subgroup. Biogen would request that 'number of SMN2 gene copies' is limited to the pre-symptomatic patient population only where SMA type cannot be assigned as symptoms have not yet presented. SMA is a heterogenous condition and whilst there are correlations between the number of SMN2 copy numbers and disease severity/ clinical course, there is substantial overlap in clinical symptoms and disease course with different copy numbers. Biogen believe functional status (non-sitter, sitter, walker) is a relevant subgroup and is aligned to the international standards of care guidelines (cite Mercuri 2018 and Finkel 2018). It is important to note that these statuses should be considered independent and not be aggregated in analyses (e.g., sitters and walkers).	Thank you for your comment. We have added "in people with pre-symptomatic SMA" to the number of SMN2 gene copies subgroup. Subgroups that are listed have been considered important but NICE understands that data limitations may mean conclusions cannot be drawn for some analyses.

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		Biogen request that NICE acknowledge there will be very limited evidence available for a subgroup of 'people who have had a prior active treatment of SMA' as prior treatment is frequently cited as an exclusion criteria for entry into pivotal clinical trials [4-6, 9, 10]) but is currently being assessed across a number of ongoing studies [11].	
	Novartis Gene Therapies, Inc.	Novartis Gene Therapies have not identified additional subgroups appropriate for consideration in the proposed MTA.	Thank you for your comment.
	Spinal Muscular Atrophy UK and Muscular Dystrophy UK	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.	Thank you for your comment. We believe it is unfeasible to define subgroups based on functional milestones. No change to scope required.
	TreatSMA	Suggested subgroups are appropriate, but we also must be mindful that in adults improvements in function are less pronounced due to prolonged deterioration. This is particularly evident with extremity functionality. Younger populations are expected to show greater positive responses from treatment due to the lack of deterioration.	Thank you for your comment.

Section	Consultee/ Commentator	Comments [sic]	Action
		This also adds complexity of expectations: Younger patients are expected to show improvements; for older patients we see increased stability and less functional decline which is still a significant benefit to those individuals and families. In addition, people with spinal fusion may not have an option to have Nusinersen. Therefore we must be very open minded about considering population as a whole, but equally take into account needs of subgroups.	
	Association of British Neurologists – Neuromuscular Advisory Group	If the evidence allows the following subgroups will be considered: • SMA type • Number of SMN2 gene copies • Functional status (non-sitter, sitter, walker) • People who have had prior active treatment for SMA We make the following comments: • Treatment commencement in adults with SMA should be considered separately. The motor system in children is still developing, and early treatment can potentially restore normal (or near normal) motor milestone attainment trajectory. In contrast, motor system development in adults is complete and the scope for returning to a normal motor milestone trajectory is more limited. However, in adults with SMA, stabilisation and/or slowing the rate of later progression is an important beneficial outcome. • The functional status of non-sitter, sitter, and walker was clearly defined in natural history studies of SMA, but with the availability of disease modifying treatments the phenotypes observed are changing. For example, a 40-year-old adult with SMA3 may have attained	Thank you for your comment. Companies can choose to analyse the data in the best way they see fit. Certain subgroups or cohorts could appear to warrant separate analyses, which the companies are free to do. No change to scope required.

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		walking, but function may now be less in the upper limbs than a person who did not attain walking. Subgroup analysis will need care in adults. • SMA4 should be included in the analysis. Whilst only affecting a small number of patients, the current lack of available treatment for these patients is based on a very arbitrary definition of "adult onset" which does not bear any real relevance to the underlying disease pathogenesis. Such patients may lose the ability to ambulate in adult life, and thus become unable to walk. Treatment may prevent such deterioration.	
	Newcastle EAG	Should subgroup by age at start of treatment (adult or paediatric) be considered?	Thank you for your comment.
Comparators	Roche Products Ltd.	As mentioned above, we do not believe a fair comparison can be made between nusinersen and risdiplam due to the substantially different patient populations and different endpoints included within the clinical trials. Within "established clinical management", we feel strongly that best supportive care should also be included as a comparator arm. Currently, neither nusinersen nor risdiplam are routinely funded for clinical practice, and as both will be re-reviewed following the end of the managed access period, there is no guarantee that either will receive a positive recommendation. This results in a risk that people with SMA may in fact go back to receiving best supportive care, as given before the introduction of nusinersen and risdiplam.	Thank you for your comment. Best supportive care has been incorporated into the scope as a comparator.
	Biogen Idec Ltd	Biogen request the term 'established clinical management' to be changed to 'best supportive care (BSC)' to better reflect the lack of routinely commissioned treatment options for certain SMA types.	Thank you for your comment. Best supportive care has been incorporated into the scope as a

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		BSC consists of multidisciplinary supportive care and follows international standards of care guidelines consisting of respiratory, gastroenterology, nutritional support, physiotherapy, orthopaedic care, assistive devices, occupational therapy and social care depending on the patient's current functional status [12, 13]. For pre-symptomatic 5qSMA, the comparators should be: • onasemnogene abeparvovec for patients likely to be diagnosed as type 1 SMA • BSC for patients likely to be diagnosed as type 2 or 3 SMA For type 1 SMA, the comparator should be: • onasemnogene abeparvovec • BSC should not be considered an ethical comparator for this patient subgroup should the patient/ parent/ guardian seek active treatment For type 2/3 SMA, the comparator should be: • BSC For each of the populations outlined above, nusinersen and risdiplam should be compared against one another where robust comparisons can be made.	comparator. For onasemnogene abeparvovec, your comment aligns with the scope.
	Novartis Gene Therapies, Inc.	Novartis Gene Therapies agree that the comparators listed in the remit are appropriate and that the list is complete. Specifically, with regard to onasemnogene abeparvovec, it is an appropriate comparator for the small and defined patient population specified by NICE and in line with the marketing authorisation. NICE recommends onasemnogene abeparvovec as a treatment option for children less than 12 months old, with 5q SMA with a bi-allelic mutation in the *SMN1* gene, either diagnosed with SMA type 1 or presymptomatic and with up to three copies of the *SMN2* gene (only if provided according to the commercial	Thank you for your comment. This detail for onasemnogene abeparvovec has been incorporated into the scope.

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		agreement with Novartis) (1). Additionally, treatment with onasemnogene abeparvovec according to NICE Highly Specialised Technologies (HST) guidance (HST 15 and 24) will be reviewed as appropriate, according to the surveillance procedure for routinely commissioned treatments.	
	Genetic Alliance UK	It is important to note that having multiple treatment options for the same condition improves patient care and outcomes. There may be certain scenarios that means one treatment option is preferred over the other. Additionally, our understanding of why some people respond better to some medications compared to others is still developing therefore having multiple options means that patients can have the best treatment option for them. This would be a good case for the committee to use all of their flexibility at their disposal to enable clinicians to provide treatment options that would best suit their patients and their families.	Thank you for your comment.
	Spinal Muscular Atrophy UK and Muscular Dystrophy UK	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.	Thank you for your comment.
	TreatSMA	Comparing both technologies to each other may not be the most productive way. In our opinion some subgroup (eg people with spinal fusion) may not have access to receive Nusinersen. It is our opinion, backed up by community, that both treatments should be made available through NHS for	Thank you for your comment.

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		clinicians to chose as per patient needs. Equally, clinicians must be given the opportunity to move patients between treatments if clinically appropriate and deemed advantageous to the patient.	
	Association of British Neurologists – Neuromuscular Advisory Group	Stated comparators are: • Established clinical management. • The interventions will be compared to each other. This is reasonable. There are no head to head randomised clinical trials of nusinersen and risdiplam so care will be needed in comparisons from MAA data as there were constraints both practical (e.g. spinal access and the early access scheme for adults and risdiplam was only for type 2 SMA) and timing (nusinersen was available earlier and then risdiplam later). These issues led to changing clinical and patient choices which will affect those currently receiving each treatment.	Thank you for your comment.
	Newcastle EAG	Eligibility for interventions and possible reasons for stopping treatment differ and factors such as local treatment offerings and patient preference may influence the interventions administered. There is likely to be skew in type and severity between patients taking each treatment (confounded by indication) so clinical appropriateness of the interventions as direct comparators should be considered. Note that the technologies will be provided in addition to 'existing clinical management' and is not a full alternative to the additional support that patients receive (such as physiotherapy, occupational therapy, orthopaedics). There may be patients who have stopped an active intervention, changed active intervention, or may have historical data under existing clinical	Thank you for your comment.

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		management, some additional clarification on whether these scenarios would be appropriate or included comparators would be beneficial.	
Outcomes	Roche Products Ltd.	Roche broadly agrees with the outcome measures stated in the draft scope but would recommend including the following additional outcome measures: ● Independence for daily activities (patient- and/or caregiver- reported) ● Impact on work productivity and activity impairment of carers of individuals with SMA In terms of specific endpoints used in our clinical studies, Roche would like to highlight that these differ across our trials for different types of SMA patients, and these differences need to be considered during the NICE appraisal process. For motor function in Type 1 SMA patients, the FIREFISH study used the Bayley scales of infant and toddler development – third edition (BSID-III) as the primary endpoint, while our Type 2/3 study used the MFM-32 as the primary endpoint. Additional secondary motor function outcomes were also considered, such as Hammersmith Infant Neurological Examination (HINE) in Type 1 patients. In comparison, the CHERISH study included a primary endpoint measuring change in baseline using the HFMSE. The differences in our specific endpoints for our clinical studies further reiterates the challenges of comparing risdiplam with nusinersen. Regarding HRQoL, the QALY and cost-effectiveness assessment in the Type 1 SMA patient population will be challenging, as there are no validated HRQoL measures for this patient population. In addition, the EQ-5D is not validated in infants. In FIREFISH, the Infant Toddler Quality of Life (ITQOL) Questionnaire was used. In SUNFISH, theEQ-5D was collected to calculate health utility scores for patients, and Work Productivity and Activity	Thank you for your comments. Your suggested additions regarding HRQoL requires no changes to the scope because these are covered under health-related quality of life. Thank you for the detail concerning trial endpoints, these will be considered in your evidence submission.

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		Impairment: Caregiver (WPAI:CG) to assess occupational work productivity and activity impairment of parents of individuals with SMA.	
	Biogen Idec Ltd	The outcomes listed are appropriate although it should be acknowledged that some outcomes (e.g. motor function) are not consistently measured using the same scales (e.g. HFMSE in CHERISH [5] and MFM32 in SUNFISH [10])	Thank you for your comment.
	Novartis Gene Therapies, Inc.	Novartis Gene Therapies recognise that all outcomes in the draft scope are important.	Thank you for your comment.
	Spinal Muscular Atrophy UK and Muscular Dystrophy UK	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 does not mean that real world evidence should not be highly valued	Thank you for your comment. We acknowledge that the available PROMs evidence will be a helpful contribution to the evaluation process. No changes to scope required.
	TreatSMA	• motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills) – *this is appropriate, as*	Thank you for your comments. Based on

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		long as it is understood that in older patients preventing further deterioration is more important than gaining scores on motor function scales. It must also be acknowledged that the level of improvements seen within the older population may be significantly smaller and not captured as part of the motor function scales, but remain significant for the individual. • bulbar function (including, for example, swallowing and ability to communicate) – *appropriate.* • frequency and duration of hospitalisation – *must be used very carefully. After pandemic and lockdowns many people have their immune system compromised and therefore it is likely that hospitalisation for patient at risk is generally on the rise. In addition, hospitalisations is one side of the coin – the speed of recovery from hospitalisation should also be considered.* • respiratory function – *is an appropriate measure, but must be viewed in the context of "no adverse events"* • complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) – *if taken out of context this can be an inappropriate measure. Contractures can arise from muscles getting stronger and lack of appropriate physiotherapy support. Patients with spinal curves may be more prevalent because they live longer, because they sit (instead of being immobile). This means that the treatments are working, but the physio support within community is not appropriate.* • need for non-invasive or invasive ventilation – *not appropriate. Patient with and without ventilations can benefit. There are other reasons that can cause patients to start ventilations.*	feedback from other stakeholders, including clinicians, we believe the current scoped list of outcomes is appropriate, and the relative significance of each may be discussed in submissions for the evaluation process proper. No change to scope required.

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		• stamina and fatigue - a*ppropriate* • mortality – *appropriate* • adverse effects of treatment – *appropriate, though these need to be identified and linked directly.* health-related quality of life (for patients and carers) – *this is very appropriate, however clarity must be given on how this is assessed. There needs to be flexibility in this measure to reflect the different expected outcomes of the different populations.*	
	Association of British Neurologists – Neuromuscular Advisory Group	Outcome measures stated: • motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills) • bulbar function (including, for example, swallowing and ability to communicate) • frequency and duration of hospitalisation • respiratory function • complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) • need for non-invasive or invasive ventilation • stamina and fatigue • mortality • adverse effects of treatment • health-related quality of life (for patients and carers).	Thank you for your comment. Your suggestions are noted and evidence from PROMs will form part of the evaluation process. No change to scope required.

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		These are reasonable as stated. The SMA REACH proforma is completed for most patients on MAA and is comprehensive. If the panel have access, harmonisation of the stated outcomes here with the SMA REACH dataset may allow easier comparison between groups: Co-morbidities, hospitalisations (recording reason for this and number of days), weight, height, SMA related surgeries, clinical trials, treatments chosen and why, adverse events, blood-test results, salbutamol use, FVC, respiratory assessments, NIV use, cough-assist use, cardiological issues, gastroenterological/nutritional issues, spine and bone health, pain management, stretching and other exercises, mental health score and interventions, social pursuits, vocational pursuits. The notable areas where the SMA REACH proforma would capture outcomes where the provided list does not are: Pain management, mental health, social interaction and vocational pursuits and these should be included. The current motor function outcome measures in the MAA are not appropriate for all adults with SMA as they measure motor milestones and do not examine smaller but functionally very important changes in motor function such as the ability to use a joystick or computer mouse – see, for example: Sansone VA, Walter MC, Attarian S, Delstanche S, Mercuri E, Lochmüller H, Neuwirth C, Vazquez-Costa JF, Kleinschnitz C, Hagenacker T. Measuring Outcomes in Adults with Spinal Muscular Atrophy - Challenges and Future Directions - Meeting Report. J Neuromuscul Dis. 2020;7(4):523-534. The number of chest infections is also useful even if they do not result in hospital admission.	

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		Number of hours of NIV required, rather than just use, or not, is also important. Patient reported outcome measures are likely to also be important particularly in adults, see, for example: Slayter J, Casey L, O'Connell C. Patient Reported Outcome Measures in Adult Spinal Muscular Atrophy: A Scoping Review and Graphical Visualization of the Evidence. J Neuromuscul Dis. 2023;10(2):239-250	
	Newcastle EAG	Is there a standard way of measuring stamina and fatigue? The measures of motor function are likely to change over time making longitudinal assessment of efficacy a challenge.	Thank you for your comment. The challenges in the evidence have been noted. No change to scope required.
Equality	Roche Products Ltd.	The SMA patient population, for which risdiplam will be a treatment option, includes babies, children and young people, as well as adults with disabilities. This will be reflected in our clinical evidence and economic analyses and should also be considered in NICE's decision-making, as per the precedent set in both NICE appraisals: nusinersen in SMA (TA588) and risdiplam in SMA (TA755) (2,3). In TA588 and TA755, the NICE committee was mindful of the need to consider whether any adjustments to its normal considerations were needed (2,3). It discussed the need to balance the importance of improving the lives	Thank you for your comment. These comments may be raised and discussed later in the evaluation process but do not specifically raise equalities issues. No

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		of children and their families with fairness to people of all ages. It noted NICE's social value judgements: principles for the development of NICE guidance, which emphasise the importance of considering the distribution of health resources fairly within society as a whole, as well as considering factors other than relative costs and benefits (6). Furthermore in both appraisals, the NICE committee also acknowledged that the SMA patient population includes people with serious disabilities, and acknowledged and considered the nature of the eligible population as part of its decision-making. Therefore, pragmatism should be taken in the interpretation of the economic case presented for this rare and very seriously debilitating condition during the decision making process, to ensure fairness of access for this population.	change to scope required.
	Biogen Idec Ltd	Aside from ensuring equitable geographic access to SMA services and treatment, there are no additional considerations.	Thank you for your comment.
	Novartis Gene Therapies, Inc.	No special considerations have been identified by Novartis Gene Therapies.	Thank you for your comment.
	Spinal Muscular Atrophy UK and Muscular Dystrophy UK	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	Thank you for your comment. We acknowledge that there may be an equalities issue relating to equitable access, and this will be investigated further in NICE's usual process. People who are included in the scope population will be

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		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.	able to access the routinely commissioned treatments. This includes all people with 5q SMA. A SMN2 copy range has been specified.
	TreatSMA	The recommendation can potentially result in inequality of access: approval for Nusinersen will exclude patients with spinal surgeries from receiving any treatment. Recommendation of Risdiplam, will potentially pose concerns in fertility for male population etc… Of course, approvals of both treatments will ensure the equal access for all. The appropriateness and choice of treatment should be down to clinical considerations between the patient and the clinician.	Thank you for your comment. We acknowledge that there may be an equalities issue, and this will be investigated further in NICE's usual process.
	Association of British Neurologists – Neuromuscular Advisory Group	All people with SMA have accessibility needs often regarding motor function and communication. There is also significant mental health burden from this long term neurological condition. See, for example: Wan, H.W.Y., Carey, K.A., D'Silva, A. *et al.* Health, wellbeing and lived experiences of adults with SMA: a scoping systematic review. *Orphanet J Rare Dis* **15**, 70 (2020). Those where English is not first language may need additional support in understanding the genetic diagnosis and the treatment.	Thank you for your comment. This does not represent an equalities issue specific to NICE's evaluation. No change to scope required.

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	Newcastle EAG	Nusinersen has additional exclusion criteria related to its route of administration (intrathecal injection) therefore may not be suitable for patients having spinal surgery for scoliosis. Also to note that patients with permanent ventilation are excluded from these treatments in the MAA.	Thank you for your comment. We acknowledge that there may be an equalities issue, and this will be investigated further in NICE's usual process.
Other considerations	Roche Products Ltd.	Economic analysis: We would like to highlight that although NICE have proposed an MTA for the appraisal of risdiplam, its assessment is anticipated to have several features that are commonly seen in the highly specialised technologies (HST) programme, therefore decision modifiers should be taken into account. This was also recognised by NICE in the appraisal of nusinersen (TA588) and the initial risdiplam appraisal (TA755), where the committee acknowledged the difficulty of appraising drugs for rare conditions (2,3) When developing the social value judgements, the Citizens Council considered that rarity alone is not a mitigating factor for accepting high ICERs, and that the committee should consider taking into account other factors such as disease severity in its decision making. In appraisals TA588, TA755 and HST15, the committee was aware that SMA is both rare and a very serious condition, and that any treatment benefits are highly valued by patients and families (2,3,9). The committee was mindful during its decision making of the need to consider whether any adjustments to its normal considerations were needed to take into account the rarity and severity of the disease.	Thank you for your comments. We note that under the current methods and processes, the company may seek to apply the Severity Modifier in its submission. No change to scope required.

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		Within SMA, there is a significant health and social care cost that is borne by families and individuals living with SMA; for example, many of the home adaptations, equipment and additional care hours are financed by the families and individuals themselves. This is a notable cost that wouldn't fall within the reference case for the costs perspective and should be taken into consideration within the evaluation of treatments for SMA.	
	Novartis Gene Therapies, Inc.	No additional considerations have been identified by Novartis Gene Therapies.	Thank you for your comment.
	TreatSMA	Appropriate	Thank you for your comment.
	Association of British Neurologists – Neuromuscular Advisory Group	NA	Thank you for your comment.
Questions for consultation	Roche Products Ltd.	**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 not currently available through a managed access agreement?** Please see the response in "Comparators" section. **What are the reasons children otherwise eligible for onasemnogene abeparvovec instead have treatment with nusinersen or risdiplam?** The outcomes data for risdiplam in the presymptomatic cohort are positive, as evidenced in the RAINBOWFISH study. If a patient is eligible for	Thank you for your comments. We will pass them to the committee to support their decision making.

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		onasemnogene abeparvovec (OA) then the decision between that and risdiplam or nusinersen would most often come down to clinician and patient choice. Whilst the therapy (OA) itself is a low burden, there are potential knock-on effects such as the need for steroid prophylaxis to manage elevated hepatic enzymes that could increase this burden. There is also a small but real risk of some serious adverse events such as liver failure and thrombotic microangiopathy. The above mentioned risks must be taken into account when deciding which therapy is most appropriate. **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? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** HRQoL assessments are particularly challenging in SMA due to the nature of the condition and the age of the patient population. There are well documented issues with conceptualising and measuring HRQoL in children and young people (7,8), which mean that QALYs may not fully capture the value of therapy. Proxy assessments of patient HRQoL may be useful and necessary in this context but may fail to provide a balanced assessment of HRQoL in SMA. The situation is further complicated by issues specific to SMA. For example, motor function may not be the only factor impacting HRQoL (i.e. improvements in motor function may not always lead to predictable improvements in HRQoL). For context, there were face validity concerns in several of the utility estimates used in the NICE appraisals nusinersen,	

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		risdiplam and onasemnogene abeparvovec (TA588, TA755 and HST15) (2,3,9). In addition, based on what is known about the disease and the burden on carers and families, it is acknowledged that a utility does not adequately capture the impact on carers and that the approach applied in the initial risdiplam appraisal understated the benefits (3). Tangible treatment benefits for this patient population include stabilisation and slower disease progression - which are considered as treatment targets for these patients. Although these benefits are desired by both clinicians and patients alike, these metrics do not translate into QALY gains, and therefore are not accounted for within the QALY calculations. Moreover, the measured changes in motor function do not account for improvements and maintained stabilisation in upper limb, bulbar and respiratory functions, all of which significantly contribute to the quality of life of the SMA population, and their caregivers. Roche is currently undertaking work to address the uncertainties within HRQoL for carers and people with SMA and how to appropriately account for the additional benefits risdiplam can offer these patients. However, due to the complexity of capturing utility data for carers and people living with SMA and accounting for stabilisation with no associated QALY gain, a pragmatic approach to understanding and applying this within the economic analysis will need to be taken by NICE and the committee. **Are the outcomes listed appropriate?** Please see the response in the “Outcomes” section.	

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		Are there any subgroups of people in whom these technologies are expected to be more clinically effective and cost effective or other groups that should be examined separately? Please see the response in the "Subgroups" section. **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 nusinersen or risdiplam are 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.** Please see the response in the "Equality" section.	

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	Biogen Idec Ltd	**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 not currently available through a managed access agreement?** See response to comparators section above **What are the reasons children otherwise eligible for onasemnogene abeparvovec instead have treatment with nusinersen or risdiplam?** Biogen believe family and clinical decision making is key to medicine choice, weighing up the efficacy and safety profile dependent on each individual patient's profile **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? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** There are challenges in measuring and valuing children's health related quality of life [14, 15], which mean that QALYs may not fully capture the value of therapy. This is further complicated in SMA due to the nature of the condition and heterogeneity of presentation. Furthermore, the benefit of nusinersen on caregivers is unlikely to be captured by the QALY calculation. In a recent review of the available	Thank you for your comment. We will pass them to the committee to support their decision making.

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		literature, caregivers to patients with SMA were placed under significant burden, including impaired HrQoL, reduced work ability, productivity and financial stress with many devoting a substantial proportion of their time to provide informal care [16]. **Are the outcomes listed appropriate?** See response to the outcomes section above **Are there any subgroups of people in whom these technologies are expected to be more clinically effective and cost effective or other groups that should be examined separately?** See response to the subgroups section above	
	Novartis Gene Therapies, Inc.	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 not currently available through a managed access agreement? If nusinersen and risdiplam were not routinely available, only a small number of patients with SMA would receive treatment with onasemnogene abeparvovec, based on the HST15 and HST24 guidance. This small and defined population includes children less than 12 months old, with 5q SMA with a bi-allelic mutation in the SMN1 gene, either diagnosed with SMA type 1 or presymptomatic and with up to three copies of the SMN2 gene. Based on epidemiological data and expert input, 35 infants with SMA type 1 could be eligible for treatment with onasemnogene abeparvovec in England each year (2, 3), while 2–3 presymptomatic infants may be identified each year as eligible through genetic testing referrals due to a family history of SMA (4).	Thank you for your comment. We will pass them to the committee to support their decision making.

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		No routinely commissioned options are available for the remaining patients with SMA (i.e. patients with SMA type 2 and 3), who would be managed with BSC based on symptoms. Whilst patients with SMA type 2 and 3 who do not receive disease-modifying therapy can reach adulthood, survival of patients with SMA type 2 is limited compared with the healthy population, ranging from 2.5–30 years (1, 2). Therefore, given the lack of routinely commissioned treatments for this population, Novartis Gene Therapies agree it is appropriate and timely to appraise nusinersen and risdiplam for the treatment of patients with 5q SMA. What are the reasons children otherwise eligible for onasemnogene abeparvovec instead have treatment with nusinersen or risdiplam? There are certain situations in which treatment with onasemnogene abeparvovec would not be administered immediately upon identification of a presymptomatic or SMA type 1 patient. One would be if the patient has a high anti-AAV9 antibody titre (>1:50). This can occur in newborns due to maternal transfer of immunoglobulins across the placenta. Onasemnogene abeparvovec uses an AAV9 capsid to deliver a stable, fully functional human SMN transgene. Therefore, until the anti-AAV9 titre is <1:50, onasemnogene abeparvovec should not be administered as the safety and effectiveness of OA in patients with higher anti-AAV9 titres is not currently known. However, anti-AAV9 antibodies typically clear during the first 4–8 weeks after birth, after which onasemnogene abeparvovec can be administered. There are currently no published data regarding the prevalence of high anti-AAV9 among newborn babies in England. However, in the SPR1NT trial (5, 6), of the 44 patients screened for inclusion and treatment with onasemnogene abeparvovec, only two were excluded due to having an anti-AAV9 antibody titre of >1:50, suggesting that the majority of those identified	

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		presymptomatically or diagnosed with SMA type 1 would not be affected by this issue. Other reasons why onasemnogene abeparvovec may not be administered immediately following diagnosis include the presence of an infection or neonatal jaundice. It should be noted that, while the label recommends careful consideration of onasemnogene abeparvovec in patients with hepatic impairment (7), there are no specific requirements around neonatal jaundice, which is not typically associated with hepatic impairment. Additionally, if patients are already receiving either nusinersen or risdiplam, parents or carers may prefer to continue with the established treatment. Parents or carers may also not want their children to be administered a gene therapy, although this is expected to be a rare scenario; in the absence of nusinersen and risdiplam, BSC would then be the only management choice available to patients. 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? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. Novartis Gene Therapies are not in a position to comment. Are the outcomes listed appropriate? Novartis Gene Therapies have no further comments. Are there any subgroups of people in whom these technologies are expected to be more clinically effective and cost effective or other groups that should be examined separately? Novartis Gene Therapies have no further comments.	

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		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 nusinersen or risdiplam are 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. Novartis Gene Therapies have no further comments. NICE intends to appraise this technology through its Multiple Technology Appraisal (MTA) process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on NICE's health technology evaluation processes is available at: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation). Novartis Gene Therapies have no strong views on the most appropriate appraisal process to be used for these technologies but recognise the rationale of NICE selecting the MTA process, given that the MAAs for nusinersen and risdiplam are either approaching completion or have been	

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		collecting data for the required time period, and given the similarity of the patient populations under review.	
	Spinal Muscular Atrophy UK and Muscular Dystrophy UK	**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 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?**	Thank you for your comments. Your concerns have been noted. No change to scope required.

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

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		• 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?** 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.	

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		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 • **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.**	

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		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.	
	TreatSMA	**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 not currently available through a managed access agreement?** There are no additional treatments available for current population who are outside of scope onasemnogene abeparvovec. Therefore approval of these treatments is essential for the community. **What are the reasons children otherwise eligible for onasemnogene abeparvovec instead have treatment with nusinersen or risdiplam?** For example children that have antibodies to AAV. Safety consideration by parents, who may not want to have children on anti-infammatory steroids for long periods of time as this can affect body in many ways. There may also be religious reasons as to why families would consider gene therapy an inappropriate treatment (similar to blood transfusion products) **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? Please identify the nature of the**	Thank you for your comments. Your concerns have been noted. No change to scope required.

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		data which you understand to be available to enable the committee to take account of these benefits. Because of the extreme variability with SMA across the spectrum flexibility and subjectivity needs to be applied. The science behind these treatments is irrefutable, they provide a mechanism for treatment. The impact of treatment must be subjective. **Are the outcomes listed appropriate?** Mostly, but see comments above. **Are there any subgroups of people in whom these technologies are expected to be more clinically effective and cost effective or other groups that should be examined separately?** SMA condition is a spectrum and it would be difficult to isolate groups specifically, due to finer points and distinctions between individuals. A newly diagnosed (ideally pre-symptomatic) child would arguably benefit the most and show best cost effectiveness. However for an adult access to treatments will be life changing! We must be pragmatic and ensure that access is available for all patients and it is up to clinician to make suitable decision in the clinic with the patient in front of them!	
	Association of British Neurologists – Neuromuscular Advisory Group	**Questions for consultation** • **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 not currently available through a managed access agreement?** o Current standards of care Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscular Disorders 28 (2018) 103–115.	Thank you for your comments. Your concerns have been noted. No change to scope required.

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		○ Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscular Disorders 28 (2018) 197-207. • **What are the reasons children otherwise eligible for onasemnogene abeparvovec instead have treatment with nusinersen or risdiplam?** ○ This needs answer from paediatric neuromuscular specialist. • **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? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** ○ It is important to note that very small differences in power and function can mean a huge amount to a person with SMA. For example, retaining some small finger movement which enables the ongoing use of a wheelchair joystick can make the difference between a life with a degree of independence versus complete dependence on others. • **Are there any subgroups of people in whom these technologies are expected to be more clinically effective and cost effective or other groups that should be examined separately?** ○ As above there will be difference in the effect on change in motor function in adults compared to children due to the	

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		natural motor development in childhood. This alters how effective treatments appear in adults but stablising or achieving small improvements in motor function when the natural history is of one of decline, are functionally extremely valuable in adult population. o Please also see comments related to SMA4 subtype. • **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 nusinersen or risdiplam are 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.** No concerns, except for the issue relating to SMA4, where marketing authorisation appears to be in place for nusinersen but not risdiplam. In our view this group of patients should not be excluded from treatment.	

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	Newcastle EAG	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? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. RESPONSE: Clinical Experts have advised that different motor function scales are used depending on age of patient and motor skill range. There is not one standardised or common motor function scale. An increase in one scoring system may have a higher impact on patient quality of life than a decreased in a different scoring system (i.e. scoring systems don't have equal weight).	Thank you for your comment. Your concerns have been noted and will be discussed during the evaluation process. No change to scope required.

Newcastle EAG have been included as a stakeholder for the consultation of this scope because they provided statistical advice to the companies (Biogen and Roche) and registries (SMA Reach UK and Adult SMA Reach) that collected data according to the Data Collection Arrangement during the managed access period.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope:

Neonatal and Paediatric Pharmacy Group (NPPG)