National Institute for Health and Care Excellence

Health Technology Evaluation

Intrathecal onasemnogene abeparvovec for treating spinal muscular atrophy in people 2 years and over [ID6556]
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	Novartis	It is appropriate for NICE to evaluate this topic, and the single technology appraisal (STA) route is also considered appropriate.	Comments noted, no action required.
	SMA REACH UK	A highly specialised technology appraisal seems more appropriate as SMA is a relatively rare and highly complex condition; the HST root may better capture the general requirements of affected patients and how treatment needs to interface with standards of care.	Comments noted. Taking into account the criteria for the highly specialised technology (HST) programme, NICE has determined that intrathecal onasemnogene should be appraised as a single technology appraisal (STA). No action required

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	MDUK	We think that this is an appropriate topic to evaluate and given the number of likely patients who could access the technology, the single technology appraisal route is appropriate.	Comments noted, no action required.
	SMA UK	Appropriate to evaluate gene therapy onasemnogene abeparvovec (OAV101 IT) delivered by a single lumber puncture into the fluid bathing the brain and spinal cord (intrathecal delivery). An STA is the appropriate route. There are alternative treatments and potentially numbers that would exceed the very rare and other eligibility criteria.	Comments noted, no action required.
	Genetic Alliance	Genetic Alliance UK welcomes the opportunity to comment on this draft scope for intrathecal onasemnogene abeparvovec (OA). In preparing our response, we have held meetings with representatives of SMA UK and SMA REACH UK. We agree that the proposal to evaluate intrathecal OA via the STA route is appropriate given the larger population compared with ultra-rare conditions appraised under the HST programme. Recent STAs for nusinersen and risdiplam also provide clear precedent for this pathway. However, we would recommend that NICE acknowledge it may be difficult for the evaluation to fully capture the distinct needs of older children and adolescents if considered identically to infants affected by SMA in its approach.	Comments noted, no action required. The NICE committee will take into consideration the challenges capturing the distinct needs of different age groups in its decision making. No action required.
Wording	Novartis	The wording of the remit is appropriate.	Comment noted, no action required.
	SMA REACH UK	The draft is quite simplified so not able to comment on wording at this stage	Comment noted, no action required.

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	MDUK	Yes	Comment noted, no action required.
	SMA UK	Yes	Comment noted, no action required.
	Genetic Alliance	The remit wording is clear and consistent with the intended marketing authorisation.	Comment noted, no action required.
Timing Issues	SMA REACH UK	By 2026	Comment noted. NICE aims to publish final guidance within 90 days of the technology receiving its UK marketing authorisation. NICE has scheduled this topic into its work programme.
	MDUK	While both nusinersen and risdiplam are currently available through Managed Access Agreements (MAA) for people over 21 kg with SMA, not everyone is able to benefit. Some people are ineligible due to strict criteria, others may be dissatisfied with their current treatment, and some have had to discontinue treatment altogether. Moreover, existing options do not target the underlying genetic cause of SMA. These treatments are also undergoing reassessment by NICE, and with the MAAs coming to an end, there is uncertainty around their future availability. This adds further urgency to the need for evaluation.	Comments noted. NICE aims to publish final guidance within 90 days of the technology receiving its UK marketing authorisation. NICE has scheduled this topic into its work programme.

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		Time is critical in SMA. Once motor neurons are lost, they cannot be repaired, making early access to disease-modifying treatments essential. Starting treatment as soon as possible helps preserve motor neurons, which can significantly improve long-term outcomes and quality of life. Given this, there is an urgent need for the NHS to ensure that all individuals with SMA have timely access to the full range of treatment options that are shown to be effective.	The committee will consider unmet need and eligibility for comparator treatment options during the appraisal. No action required.
	SMA UK	Fairly urgent. Despite alternative medications being available for people living with SMA in the UK, we would want it to take place as soon as it receives marketing authorisation because: 1. It is a therapy many have been waiting for as it is a single treatment as opposed to the other two currently available. 2. It is less of a cost and staffing burden on the health care providers than the repeated lumber punctures / prescriptions as needed for nusinersen. 3. In the case of risdiplam, it reduces the burden on patients and caregivers, who are responsible for storing, handling and administering a very expensive product. 4. This is the only SMN1 targeting therapy potentially available to this patient population.	Comments noted. NICE aims to publish final guidance within 90 days of the technology receiving its UK marketing authorisation. NICE has scheduled this topic into its work programme. The committee will consider unmet need and the costs and benefits compared to comparator technologies during the appraisal. No action required.
	Genetic Alliance	It is our view that this evaluation is urgent. Families affected by SMA have expressed concern that delays may result in irreversible progression and loss	Comments noted.

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		of function in children and young people living with SMA while they wait for new therapeutic options to be made available. A timely appraisal would also reduce inequities between infants, who can already access intravenous gene therapy, and older children who currently cannot. We also note that the UK National Screening Committee (UK NSC) is preparing for an in-service evaluation of newborn screening for SMA, and alignment with this developing policy and its implementation is anticipated to be very important.	NICE aims to publish final guidance within 90 days of the technology receiving its UK marketing authorisation. NICE has scheduled this topic into its work programme. The committee will consider unmet need and equalities issues during the appraisal. No action required.
Any additional comments on the draft remit	Genetic Alliance	There are a number of advantages that intrathecal OA offers compared to nusinersen and risdiplam. For example, intrathecal OA may be used as a single treatment (unlike nusinersen and risdiplam) and help avoid the need for repeat lumber punctures and prescriptions (which are required for nusinersen). Importantly, it is also the only SMN1 targeting therapy potentially available to this patient population. It our view that a managed access agreement (MAA) approach for intrathecal OA would be appropriate, to enable broad but carefully monitored early access and enable more data collection on the condition. However, it will be important to ensure consistency with ongoing MAA reviews for nusinersen and risdiplam to avoid the risk of care pathways becoming fragmented for families affected by SMA.	Comments noted. The committee will consider the benefits of intrathecal onasemnogene abeparvovec, including any which are not sufficiently captured in the economic modelling, in its decision making. The committee will consider a managed

Section	Stakeholder	Comments [sic]	Action
			access agreement if appropriate.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Novartis	Novartis suggest the following updates (shown in bold and underlined) are made to the *Background section* to improve the clarity and accuracy of the content: **Current wording:** "SMA causes substantial disability, and may lead to increased mortality and reduced life expectancy." **Suggested wording:** "SMA causes substantial disability, and **usually** lead**s** to increased mortality and reduced life expectancy **without intervention**." **Rationale:**	Comments noted. The background section of the scope provides a brief overview of the disease. The scope has been updated to reflect the suggested changes as appropriate.

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		Without intervention, the majority of spinal muscular atrophy (SMA) types result in increased mortality and reduced life expectancy, with the only exception being Type 4 patients who may live to normal life expectancy. **Current wording:** "SMA symptom severity varies substantially and is often grouped into SMA types based on the age of onset of symptoms and the best motor function the person obtained" **Suggested wording:** "SMA symptom severity varies substantially. **Historically, SMA was** grouped into types based on the age of onset of symptoms and the best motor function the person obtained. **However, with the availability of disease modifying treatments (DMTs), SMA exists on a broad continuum, with overlap in symptoms and outcomes across these historical SMA types."** **Rationale:** The historical classification of SMA by type no longer adequately describes outcomes for patients treated with DMTs, which have altered the disease trajectory, leading to the emergence of functional phenotypes[4]. Through treatment with DMTs, people with SMA are now able to achieve more motor milestones and functional abilities than would be predicted based on historical type classifications[5]. **Current wording:** "The number of *SMN2* gene copies, which encodes the SMN protein that can partially compensate for the loss of the *SMN1* gene..." **Suggested wording:** "***SMN2* is a back-up gene, a low-functioning paralogue of *SMN1* which can partially compensate for the loss of the *SMN1* gene[6]. It is well established that *SMN2* is less efficient at producing SMN protein, with only 10–15% of the protein produced by**	

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		***SMN2* being full-length, functional SMN proteins[7-10]. As a result,** the number of *SMN2* gene copies..." **Rationale:** For improved clarity. The current wording could be interpreted to mean the *spinal motor neuron 1 (SMN1)* and *spinal motor neuron 2 (SMN2)* genes produce different SMN proteins, which is not the case. The same protein is produced by both genes, but *SMN1* is the primary and optimal source of the SMN protein, whereas *SMN2* typically produces non-functional proteins[7-10]. In *The technology section:* **Current wording:** "It has been studied in clinical trials for treating 5q SMA in people aged 2 - 17 years." **Suggested wording:** "It has been studied in clinical trials for treating 5q SMA in people aged 2 - **<18** years." **Rationale:** To align with the official age group used in the STEER and STRENGTH trials. **Current wording:** "Onasemnogene abeparvovec as an intravenous infusion has a marketing authorisation in the UK for the treatment of • people with 5q SMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1, or • people with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene." **Suggested wording:** Novartis propose that these paragraphs are removed. **Rationale:**	

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		A separate marketing authorisation application is being submitted for onasemnogene abeparvovec as an intrathecal injection. This is not an extension of the marketing authorisation for the intravenous (IV) infusion of onasemnogene abeparvovec. As such, whilst Novartis acknowledges this concerns the same molecule, the marketing authorisation information for the IV formulation is not relevant in the context of this submission.	
	SMA REACH UK	SMA is described in lay language.	Comment noted. No action required.
	MDUK	For type 2 SMA it could be made clearer of its severity. We suggest this description: • 'In SMA Type 2 the onset of symptoms is between 7 and 18 months of age. People with this condition are often severely disabled **and are unable to stand without support. They are never able to walk unaided.**' The differences in life expectancy could be clearer. We suggest this description: • 'The most severe type of SMA, Type 1, if untreated, typically leads to death before age 2 years. SMA Type 2 may shorten life expectancy, while life expectancy for SMA Types 3 and 4 aligns with the general population.' It is also worth noting that an in-service evaluation of newborn screening for SMA has been commissioned, which could lead to its introduction in the near future and enable earlier diagnosis and treatment. Treatment decisions would be based on genotype rather than clinical phenotype, focusing on SMN1	Comments noted. The background section of the scope provides a brief overview of the disease. The scope has been updated to reflect the suggested changes as appropriate.

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		homozygous deletions and SMN2 copy number (typically between 1 and 4 copies). As there is already overlap between SMN2 copy number and clinical presentation, traditional SMA type classifications are already becoming less relevant.	
	SMA UK	**Edits in red** **Paragraph 1** ***1. Increasing accuracy of description of 5Q label:*** Spinal muscular atrophy (SMA) is a rare neuromuscular genetic disorder that causes muscle weakness and progressive loss of movement. It is most commonly caused by defects in the gene SMN1, <u>located on the 5th chromosome labelled q which is why it is correctly called 5q SMA. It leads to degeneration of motor neurones in the spinal cord (this is termed '5q SMA').</u> ~~which leads to degeneration of motor neurones in the spinal cord (this is termed '5q SMA').~~ The motor neurones most affected by this condition are those that allow walking, crawling, arm movement, head and neck movement, swallowing and breathing. SMA causes substantial disability, and may lead to increased mortality and reduced life expectancy. ***2. There are different forms of SMA that have a different genetic cause, they are not within the scope – differences in severity of 5Q SMA are known as 'types'.*** The most severe ~~forms~~ <u>types</u> of SMA, if untreated, typically causes death before age 2 years. People with later-onset types of SMA usually live into adolescence or adulthood. SMA also has substantial effects on families and carers, including the impact of caring for the patient, the need for specialist equipment and ongoing emotional, financial and social impacts.	Comments noted. Please note that edits originally shown in red are now presented in black text and underlined (where relevant) for accessibility and clarity. The background section of the scope provides a brief overview of the disease. The scope has been updated to reflect the suggested changes as appropriate.

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		Paragraph 2 1. ***Clarity that this 'type' diagnosis is not a genetic one and is dependent on the opinion of the diagnosing clinician and the medical history that they are given.*** SMA symptom severity varies substantially and is often grouped into SMA types by a clinician at diagnosis based on the age of onset of symptoms and the best motor function the person obtained. The types of SMA decrease in severity from type 0, in which symptoms arise before birth and babies survive for only a few weeks, to type 4 (adult-onset) which is associated with mild motor impairment and a normal life span. Categorising people into types consistently at presentation is difficult due to the variable nature of the disease. 2. ***Clarity on the level of disability experienced by people living with type 2 SMA, without using the generic term 'severely disabled' which may be open to individualised interpretations.*** Types 0 and 4 are rarely diagnosed and therefore there is little evidence for these types. In people with type 1 SMA, symptoms arise before 6 months and babies are unable to sit independently; babies with type 1 SMA have low muscle tone (hypotonia) and severe muscle weakness which affects movement, swallowing and breathing. In people with type 2 SMA, the onset of symptoms occurs at between 7 and 18 months People with type 2 SMA are unable to walk, and, if not treated early on, are powerchair users. Most have weak breathing, chewing and swallowing muscles as well as weak upper limb movement and scoliosis all of which require significant interventions, ~~and~~	

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		~~people with this condition are often severely disabled and unable to walk unaided.~~ People with type 3 SMA experience varying degrees of symptom severity with muscle weakness appearing between age 18 months and 18 years. Most people with type 3 SMA can walk or sit unaided at some point in their lives however, ~~but many lose mobility over time~~. many become powerchair users and can be severely impacted by the condition[1] **Paragraph 5** **In addition:** In 2021, NHS England approved funding for a gene therapy treatment for children who have SMA Type 1 who are over 12 months old and within the scope of the drug's European Medicines Agency (EMA) marketing authorisation. Most of these children have now been assessed for treatment by the NMDT who were required to assess and approved treatment for this cohort of children. (Reference: NHS England Communication 8th March 2021 >) Children treated via this route must weigh less than 21 kgs.	
	Genetic Alliance	To our understanding, the background information is accurate and describes the natural history and burden of SMA well. We suggest clarifying that the population for intrathecal OA includes older children and adolescents (2–17 years) who were excluded from the intravenous licence, as this contextualises a clear area of unmet need that the availability of this therapy via the NHS seeks to address.	Comments noted. The title, remit and population in the draft scope have been updated to reflect that the population for this appraisal is people aged 2 years and older.

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Population	Novartis	Novartis suggest the population definition is amended to state “People with 5q spinal muscular atrophy [redacted]”, [redacted]	Comment noted. The population in the scope has been updated to include ‘2 years and over’.
	SMA REACH UK	Quite simplified lay language Clarify the age range (suggested >2 years of age)	Comments noted. The population in the scope has been updated to include ‘2 years and over’.
	MDUK	The population should be in line with the marketing authorisation for this formulation, which we believe is people with 5q SMA over the age of two.	Comments noted. The population in the scope has been updated to include ‘2 years and over’.
	SMA UK	Yes	Comments noted. The population in the scope has been updated to include ‘2 years and over’.
	Genetic Alliance	The scope identifies people with 5q SMA appropriately. However, clinical classification by SMA type alone may be misleading. To our understanding from speaking with members of the community and clinicians involved in caring for children with SMA, in some cases, the type of SMA diagnosed may	Comments noted. The background section of the scope has been updated to reflect that

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		be arbitrary and inconsistent, and that functional status and SMN2 copy number may provide more equitable definitions. We therefore recommend avoiding overly rigid type-based labels in favour of a spectrum-based description, and considering other areas where more flexibility will be needed.	while SMA has historically been grouped into types, with the availability of disease modifying treatments, SMA exists on a broad continuum, with overlap in symptoms and outcomes across the SMA types. The population has also been updated to include '2 years and over'.
Subgroups	Novartis	Novartis does not consider it is appropriate to explore the following subgroup analyses from the studies of intrathecal onasemnogene abeparvovec: • Number of *SMN2* gene copies • Functional status (non-sitter, sitter, walker) • SMA type These subgroups would be associated with small patient numbers, and it would therefore not be appropriate to draw conclusions from such analyses given the level of uncertainty. In addition, the overlap in disease severity between SMA subgroups (highlighted in the comments in the *Background* section) makes the historical SMA type subgroup comparisons unsuitable.	Comments noted. NICE understands that data limitations may mean conclusions cannot be drawn for some analyses. The company is invited to provide rationale for not including any subgroups in its submission.
	Roche	The age at onset of SMA symptoms and the duration of symptoms prior to initiation of therapy should be documented as this will have an impact on outcomes and response to therapy.	Comments noted.

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		Additionally, the duration and age at initiation of the prior disease modifying therapy should be documented, as well as the reason for switch - loss or lack of efficacy, access issues, patient or family choice, or side effects.	The scope has been updated to include 'Age of symptom onset' in the list of subgroups.
	SMA REACH UK	The population to target would be mainly SMA type 2 and 3 and pre-symptomatic. (potentially including adults should the label encompass this population); With the implementation of newborn screening, classification by type may make this less relevant and so this should be clarified. Potentially it could be considered for patients with a weight of >21kg who have not received IV gene therapy.	Comments noted. No action required
	MDUK	The subgroups listed are appropriate.	Comment noted
	SMA UK	No The SMA type classification is outdated and inconsistent, therefore it should not be used to create subgroups.	Comments noted. Eligibility for comparator treatments may be determined by type, so 'SMA type' remains a relevant subgroup for consideration.
	Genetic Alliance	The suggested subgroups are appropriate. We would highlight that families and clinicians consider flexibility essential, as the eligible population may extend beyond those studied in trials. For example, pre-symptomatic children identified through newborn screening may represent a subgroup of particular interest, and based on the community's experience, we would caution against excluding those diagnosed later in childhood or even early adulthood who	Comments noted. No action required

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		would have missed out on the opportunity for other potentially life-altering therapies due to a lack of a newborn screening in place to facilitate earlier diagnosis	
Comparators	Novartis	Novartis disagree with the inclusion of onasemnogene abeparvovec (IV, henceforth referred to as OAV IV) as a relevant comparator to onasemnogene abeparvovec (intrathecal injection, henceforth referred to as OAV IT). As per HST15[11], OAV IV is recommended by NICE for treating 5q SMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of type 1 SMA in babies, only if: • they are 6 months or younger, or • they are aged 7 to 12 months, and their treatment is agreed by the national multidisciplinary team In addition, it is recommended for treating presymptomatic 5q SMA with a biallelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene in babies aged 12 months and under (HST24)[12]. The anticipated marketing authorisation of OAV IT is for patients with 5q SMA [redacted]. As such, patients who would be eligible for OAV IT ([redacted]) [redacted] it is not appropriate to compare OAV IT and OAV IV within the scope of this appraisal.	Comments noted. The list of comparators is intended to be broad. The appraisal committee will discuss the most appropriate comparator(s) during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, the clinical and cost-effectiveness evidence and current clinical practice.
	SMA REACH UK	All current treatment choices are listed as comparators so don't think any additional relevant have been excluded.	Comments noted.

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		Yes. Comparisons should be made with clinical trials and real-world data on nusinersen and risdiplam.	The list of comparators is intended to be broad. The appraisal committee will discuss the most appropriate comparator(s) during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, the clinical and cost-effectiveness evidence and current clinical practice.
	MDUK	We believe the marketing authorisation will cover people with SMA over the age of two. As onasemnogene abeparvovec (intravenous infusion) is only available for a limited population (type 1 SMA, up to 12 months) there will be minimal overlap between the two populations. Therefore, we do not believe it should be considered as a comparator.	Comments noted. The list of comparators is intended to be broad. The appraisal committee will discuss the most appropriate comparator(s) during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, the clinical

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			and cost-effectiveness evidence and current clinical practice.
	SMA UK	Yes (Although Spinraza and Risdiplam are currently under a MAA, and as so are not fully approved by the NHS.)	Comments noted.
	Genetic Alliance	The comparators listed reflect current NHS practice. Nusinersen and risdiplam are available via managed access, intravenous OA is available for infants under HST guidance, and best supportive care remains relevant. However, it may be difficult in practice to compare intrathecal OA directly with intravenous gene therapy, as the eligible populations may differ. Families have also raised concerns about the tolerability of existing therapies, including chronic gastrointestinal side effects and difficulties with frequent lumbar punctures, which make an alternative intrathecal option particularly valuable and have a positive impact on the quality of life for these children and young people.	Comments noted. The list of comparators is intended to be broad. The appraisal committee will discuss the most appropriate comparator(s) during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, the clinical and cost-effectiveness evidence and current clinical practice.

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Outcomes	SMA REACH UK	All outcome listed are of interest and look at different areas (motor, bulbar, respiratory, mortality etc). What is not clearly detailed is what information will be collected for Bulbar/ Communication as there are currently no established protocols. For example, the bulbar should include CEDAS score. Looking at stamina and fatigue could be done as a sub-research project as there are no current agreed tools for these aspects. All this info is relevant but could add burden on clinical appointments/ services and patients. This needs to be taken into consideration and appropriate resources made available. Speech/communication is relevant for SMA type 1 mainly. These need to be grouped more succinctly. motor together, respiratory together etc. They also talk about respiratory function with no clarity around what they intend to include in this. There needs to be more detail around ventilation and usage. There is no mention of airway clearance requirements either.	Comments noted. The list of outcomes provides a summary of main outcomes and is not intended to be an exhaustive list. NICE does not specify which measurement tools should be used for each outcome. No action required. The stakeholder is invited to discuss the relative significance of each outcome in its submission.
	MDUK	This appears to be a comprehensive list. There are other outcomes which are important for people with SMA, however these can be more difficult to measure quantitatively. For example: • Maintenance or stabilisation of condition • Impact on education, ability to work and socialise • Independence As this could be another treatment option for people with SMA, it is also important to think consider patient choice. Especially when patients may not be satisfied with the current treatments (nusinersen and risdiplam, under MAA). For example, they may prefer to take a ‘one time’ treatment compared	Comments noted. The list of outcomes provides a summary of main outcomes and is not intended to be an exhaustive list. Some of the additional outcomes mentioned are covered by health-related quality of life. Stabilisation of disease will be also be considered as part of

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		to taking an oral treatment every day (risdiplam) or having an intrathecal injection every four months (nusinersen). See also the section “Questions for consultation” for more comments on outcomes.	the listed outcomes. No action required.
	SMA UK	Yes. Fine motor skills are also measured. Although a hugely important outcome, it is very difficult to measure fatigue and stamina with any standardised measure. Data from Patient Reported Outcome Measures (PROMS) are hugely valuable if collected consistently using robust methods.	Comments noted. The list of outcomes provides a summary of main outcomes and is not intended to be an exhaustive list. The company is invited to include additional outcomes in its submission if appropriate. No action required.
	Genetic Alliance	To our understanding from discussions with the community and clinicians involved in care of people living with SMA, the draft outcomes may not fully reflect what is clinically meaningful or practically measurable in older children. Clinicians noted that not all validated motor scales apply across the SMA spectrum, and families report that swallowing, bulbar function and stamina are often more important than small motor gains. Fatigue in particular is described as a major burden but is not captured by validated instruments and they recommend this should be treated as exploratory rather than a primary outcome that underpins a decision by NICE. Further, orthopaedic complications, such as scoliosis, are expected in this population and should not necessarily indicate that the treatment is not effective. Patient- and carer-	Comments noted. The list of outcomes provides a summary of main outcomes and is not intended to be an exhaustive list. Based on comments from other stakeholders, we believe the current scoped list of outcomes

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		reported outcomes are highly important to uncover some of these nuances, and these require consistent data collection and further investment in registry infrastructure to ensure they are robust for appraisal.	is appropriate, and the relative significance of each, and difficulties measuring these outcomes, may be discussed in submissions for the evaluation process. The company is invited to include additional outcomes in its submission if appropriate. No change to scope required.
	British Orthopaedic Association (BOA) and British Society for Children's Orthopaedic Surgery (BSCOS)	Outcomes to be included: 1. Musculoskeletal Pain (i.e. hip pain) 2. Development of scoliosis 3. Hips displacement	Comments noted. The list of outcomes provides a summary of main outcomes and is not intended to be an exhaustive list. The company is invited to include additional outcomes in its submission if appropriate. No action required.
Equality	Novartis	No equality issues have been identified.	Comment noted.

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	SMA REACH UK	Resources to tertiary centres have not been made available following the availability of multiple therapeutic options for SMA patients and a progressive growth of the patient population who now survives, while in the past the mean age at death for SMA1, the most prevalent population, was only 9 months. If new assessments/questionnaires or tests need to be implemented, it is important that as many UK NM centres are in an equal position to offer treatments and follow-ups. The Committee should have access to the distribution of patients across the country and ensure that NHS funds adequate number of sites to equitably deliver the technology to patients and monitor its effects and consider that for many patients the infusion centres and the long term monitoring .	Comments noted. Committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population during the appraisal process. No action required.
	MDUK	As this treatment is administered via intrathecal injection, it is essential that no one misses out due to a lack of facilities or clinical capacity. All eligible patients should be able to access it, regardless of where they live. Given that people with SMA often experience varying levels of disability, it's also important that they are not required to travel long distances to receive the treatment. At the same time, delivery must be safe and effective, which means having specialist staff and appropriate infrastructure in place. This balance between accessibility and clinical feasibility will inevitably influence which sites are able to offer the treatment, but the overarching priority must be to ensure equitable access for all.	Comments noted. Committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population during the appraisal process No action required.
	SMA UK	No changes needed	Comments noted, no action required.

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Other considerations	Roche	"*Nusinersen for treating spinal muscular atrophy (2023) NICE technology appraisal guidance 588*" guidance should be dated 2019 not 2023. "*Onasemnogene abeparvovec for treating spinal muscular atrophy (2023) NICE Highly specialised technologies guidance 15. Review date not stated*" HST15 guidance should be 2019	Comments noted. The dates for these related NICE recommendations have been updated as appropriate.
	SMA REACH UK	Consider the systematic collection of post-marketing adverse effects in comparison with the other approved standard treatments	Comments noted, no action required.
	MDUK	We feel that a managed access agreement should not be ruled out.	Comment noted. The committee will consider whether a managed access agreement is appropriate for this technology.
	SMA UK	No other considerations	Comment noted
	Genetic Alliance	Genetic Alliance UK works closely with a number of stakeholders in the SMA community and understands there may be a few considerations around equality to note in this evaluation. Firstly, young people with SMA may experience challenges when transitioning between paediatric and adult services, which is often known to lead to discontinuities in access to specialist care for people living with rare conditions.	Comments noted. Committee will consider whether its recommendations could have a different impact

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		Intrathecal delivery requires specialist anaesthesia and, in some cases, interventional radiology, which may not be uniformly available across centres. We also heard that geography and socio-economic position can influence a family's ability to attend specialist centres for repeated assessments or intrathecal administration, which may deepen existing inequalities. To our understanding, weight and spinal deformity may limit feasibility for some children, raising concerns about fairness if these groups are excluded. Families with children who have bulbar impairment also told us that standard outcome measures can be inaccessible, meaning some groups risk being under-represented in trial and registry data. We recommend that NICE consider how managed access could address these uncertainties, and that evidence requirements are linked with existing SMA registries and NHS datasets to capture long-term outcomes, safety, and carer experiences consistently.	on people protected by the equality legislation than on the wider population during the appraisal process. Committee will also consider whether a managed access agreement is appropriate for this technology.
Questions for consultation	Novartis	**Where do you consider intrathecal onasemnogene abeparvovec will fit into the existing care pathway for SMA?** **Response:** Novartis expect that OAV IT will be a switch therapy for patients with 5q SMA [redacted], providing an alternative treatment for patients currently treated with nusinersen or risdiplam. It will not be used as an add-on treatment. Those previously treated with an IV infusion of onasemnogene abeparvovec will not be eligible for treatment with the intrathecal injection. **For people already on treatment, what may prompt switching to intrathecal onasemnogene abeparvovec?**	Comments noted. No action required.

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		Response: Currently available treatments for SMA in the UK require chronic administration, either through daily oral administration (risdiplam) or regular intrathecal injections (nusinersen), often posing a substantial burden to patients and their caregivers in terms of time, pain, and, travel; leading to challenges with adherence to the recommended dosing schedules. Real-world data indicate frequent deviations from dosing schedules result in a negative impact on health outcomes, and increased healthcare resource use (HCRU)[13-15]. In particular, the need for repeated intrathecal administration of nusinersen, which may require sedation, is particularly challenging for patients, caregivers, and healthcare services[16, 17], as it can increase the risk of headache, backache, infection, cerebrospinal fluid (CSF) leakage, and exacerbations of respiratory function impairment[18]. Those with scoliosis face further challenges, as repeated intrathecal administration often necessitates the use of ultrasound, fluoroscopy, or other imaging techniques, which can involve high cumulative radiation exposure with repeated administration[5, 19]. Respiratory and bulbar function issues may be exacerbated by scoliosis, also complicating the daily dose requirements for risdiplam[20, 21]. Given these challenges, the reduced burden offered through one-time treatment with onasemnogene abeparvovec through a single intrathecal injection may prompt clinicians to recommend switching treatment from risdiplam or nusinersen to OAV IT. In addition, people with SMA and their caregivers who are unsatisfied with the experience on current treatments may wish to switch to OAV IT. Reasons for this may include: • Declining motor function: Recent long-term clinical data for symptomatic patients with later-onset SMA treated with *SMN2*	

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		splicing modifiers show a decline in motor function improvements over time, with Hammersmith Functional Motor Scale Expanded (HFMSE) scores returning to baseline and falling below it after 4–6 years of treatment[22, 23] • Adverse effects: Risdiplam may have harmful effects on the foetus when administered to pregnant women, and may also compromise male fertility[17, 24-26]. **Please select from the following, will intrathecal onasemnogene abeparvovec be:** **A. Prescribed in primary care with routine follow-up in primary care** **B. Prescribed in secondary care with routine follow-up in primary care** **C. Prescribed in secondary care with routine follow-up in secondary care** **D. Other (please give details):** **Response:** Option C, OAV IT will be prescribed in secondary care with routine follow-up in secondary care. **For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.** **Response:** Prescription and routine follow-up for comparator treatments also takes place in the secondary care setting.	

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		Would intrathecal onasemnogene abeparvovec be a candidate for managed access? **Response:** Novartis prioritise access to treatment for people with SMA, therefore, if managed access has the potential to help resolve a key uncertainty raised as part of the appraisal, Novartis would be willing to consider this. **Do you consider that the use of intrathecal onasemnogene abeparvovec can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** **Response:** Yes. As highlighted in the external assessment group (EAG) report for the multiple technology appraisal (MTA) of nusinersen and risdiplam (ID6195), EQ-5D, the preferred measure of HRQoL, may not adequately capture the nuanced treatment benefits observed in people with SMA, such as improvements in quality of life (QoL) within each motor milestone, given its generic nature[27]. These important improvements can include holding objects, lifting toys, even the ability to achieve basic movements such as lifting a single finger can be extremely important to a wheelchair user, allowing them improved motor control, and granting them some level of independence. Similarly, as noted in the draft scope, SMA has substantial effects on families and carers, including the impact of caring for the patient, the need for specialist equipment and ongoing emotional, financial, and social impacts. Whilst caregiver HRQoL will be considered within the outcomes of this appraisal, this is not expected to adequately capture the burden of caregiving,	

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		which extends beyond HRQoL alone. In addition, the EQ-5D tool was not designed for caregivers, and instead focusses on physical health, potentially leading to the benefits of treatment being underestimated[28, 29]. OAV IT offers the potential for substantially reduced burden for both people with SMA and carers due to its one-time administration, in contrast to the chronic treatments currently available, which require regular intrathecal administration, in the case of nusinersen, or daily oral administration, in the case of risdiplam, the chronic nature of which may serve as an ongoing reminder to patients and their carers of their diagnosis. Furthermore, the benefits of gene therapy often extend beyond health benefits, as highlighted by the committee in the appraisal of voretigene neparvovec (HST11), who noted that the treatment was expected to reduce expenditure by non-NHS government departments that provide support for families affected by the disorder[30]. Similarly, societal costs which may be lessened through treatment, such as patients' and caregivers' ability to work or attend school, and personal costs for travel and modifications to homes, will not be captured in the base case quality adjusted life years (QALY) calculations, given they fall outside of the NICE reference case[28]. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** **Response:** Whilst Novartis expect data on HRQoL for both patients are carers to be limited, we will endeavour to identify the most appropriate inputs for the analysis from the systematic literature review (SLR) and will present various scenarios to account for any uncertainty resulting from data limitations.	

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		Additionally, the inclusion of societal costs will be explored in a scenario analysis, subject to data availability. **Please indicate if any of the treatments in the scope are used in NHS practice differently than advised in their Summary of Product Characteristics. For example, if the dose or dosing schedule for a treatment is different in clinical practice. If so, please indicate the reasons for different usage of the treatment(s) in NHS practice. If stakeholders consider this a relevant issue, please provide references for data on the efficacy of any treatments in the pathway used differently than advised in the Summary of Product Characteristics.** **Response:** Not to our knowledge.	
	MDUK	**For people already on treatment, what may prompt switching to intrathecal onasemnogene abeparvovec?** Current SMA treatments are lifelong and can be considered burdensome by some patients – requiring either daily administration or regular hospital visits every four months. Families have shared that it's easy to accidentally drop the daily treatment bottle, which can be costly for the NHS and stressful for families to resolve. Some individuals may also feel that their current treatment isn't making a meaningful difference and may wish to explore alternative options. Intrathecal onasemnogene abeparvovec offers a one-time treatment approach, which could be appealing to those seeking a less demanding and potentially more effective solution.	Comments noted. No action required.

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		Ultimately, people living with SMA and their families should have the choice. They deserve the opportunity to consider all available options and make informed decisions about their care – based on what works best for their individual circumstances, preferences, and experiences. **Do you consider that the use of intrathecal onasemnogene abeparvovec can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Yes, there are several important health-related and societal benefits that are unlikely to be fully captured in the QALY calculation. These often relate to areas where data is limited – either because SMA is a rare condition or because it is difficult to generate robust quantitative evidence. This has already been acknowledged in the ongoing MTA for risdiplam and nusinersen, where the EAG report identified a significant number of qualitative considerations. While these factors are deeply meaningful to people living with SMA and their families, they are often underrepresented in QALY and ICER calculations. These aspects can have a profound impact on daily life and long-term wellbeing and should be considered as part of the broader value of treatment, even if they are not easily quantified in traditional health economic models. These include: • Maintenance or stabilisation of the condition • Impact on education, ability to work, and social participation • Increased independence • Bulbar and respiratory function • Psychological wellbeing • Patient choice and autonomy	

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		• Quality of life for carers and family members • Improvements in stamina and reduction in fatigue Beyond individual health outcomes, there are also broader societal benefits that may not be reflected in standard health economic models. These include reduced reliance on social care and support services, improved ability for parents and carers to remain in employment, and greater participation in education and community life for people with SMA. These wider impacts contribute to a more inclusive and economically active society and should be considered as part of the overall value of treatment.	
	SMA UK	**Questions for consultation** **Where do you consider intrathecal onasemnogene abeparvovec will fit into the existing care pathway for SMA?** Intrathecal onasemnogene abeparvovec **s**hould not be restricted to clinical trial population only - in view of: • The difficulties in conducting the trial – i.e. The study included treatment-naïve people between the ages of 2 and 17 with SMA Type 2, who could sit but had never walked independently. A sham-controlled study would be unethical in countries where treatments are available. For this reason, this trial did not operate in the UK or mainland Europe. It was offered in countries where no treatments were available. • The difficulties with diagnosis using type and the spectrum of SMA – SMN2 copies should also be considered • The fact that trials invariably focus on children where outcome measures are more easily mapped.	Comments noted. No action required.

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		We would like to see intrathecal **onasemnogene abeparvovec** available as an option for anyone aged 2+ (or over 21kg) living with SMA who could have a treatment delivered by lumber puncture, does not have AAV9 antibodies and has not had previous treatment with IV onasemnogene abeparvovec: -**who has** previously been treated with nusinersen or risdiplam. -**who has not** previously been treated with nusinersen or risdiplam. **For people already on treatment, what may prompt switching to intrathecal onasemnogene abeparvovec?** • Preference for a single dose compared to ongoing treatment. A single treatment is preferable to many living with SMA due to the reduced impact on daily living and increased freedom to travel. • Negative side effects to current treatments, reported issues include gastrointestinal issues, rashes, increased pain and fatigue and post-intrathecal headaches. • Non-response to the currently available treatments. • Some may prefer a treatment that targets the SMN1 gene, giving increased scope for protentional dual therapies in the future. • Some people prefer the option of an intrathecal treatment as they consider it to be one that is more targeted to the area most affected.. Some currently on Spinraza do not want to switch to Risdiplam for this reason, but would be willing to switch to an alternative intrathecal treatment. This is particularly true for those who may not be able to receive Spinraza long term due to scoliosis progression requiring surgery.	

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		• **Please select from the following, will intrathecal onasemnogene abeparvovec be:** A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care C. **Prescribed in secondary care with routine follow-up in secondary care** Monitoring by experts essential D. **Other (please give details):** **Or Prescribed in secondary care with routine follow-up in secondary care and primary care (community physio, SLT etc)** **For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention**. Prescribing and routine follow-up for Spinraza and Evrysdi differ significantly from Zolgensma, primarily because their administration is less specialised and occurs more frequently. There would need to be an increased amount of infusion centres (RNMC)to ensure geographical equity of access for both paediatric and adult patients. This would also ensure accessible follow up care. **Spinraza (nusinersen)** • **Prescribing and Administration:** Like the intervention, Spinraza is an injectable treatment administered intrathecally. This procedure requires a highly trained healthcare professional with experience in performing lumbar punctures. It is performed in a RNMC with this expertise Regional Neuromuscular Centres (RNMCs) – SMAUK	

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		sometimes under tha general anaesthetic but more commonly with a local anaesthetic cream. • **Dosing Schedule:** Treatment begins with a series of four "loading doses" over approximately two months, followed by a "maintenance dose" every four months. • **Routine Follow-up:** Because each dose requires a specialised procedure, routine follow-up is integrated into the administration schedule. Patients return to the RNMC every four months for their maintenance dose, at which time their motor function is assessed, and any adverse events are monitored. Blood and urine tests are also conducted at baseline and prior to each dose to monitor for potential side effects, such as a decrease in platelet count or kidney toxicity. **Evrysdi (risdiplam)** • **Prescribing and Administration:** Evrysdi is an oral medication that can only be prescribed by an RNMC, taken once daily at home. The powder is constituted by a healthcare professional before it is dispensed to the patient. Patients and caregivers are provided with an oral syringe and instructions on how to prepare and administer the daily dose. • **Dosing Schedule:** It is taken orally once a day with a meal at approximately the same time each day. The daily dose is determined by the patient's age and body weight. • **Routine Follow-up:** Follow-up for Evrysdi is less frequent and can often be managed through a combination of in-person clinic visits and remote care. The setting for follow-up is generally the patient's local or regional neuromuscular centre, with support from their primary care physician. Monitoring focuses on tracking the patient's weight to ensure the correct dosage and assessing for any side effects, which	

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		can include diarrhea or rash. This home-based administration model provides greater flexibility for patients and their families. **Would intrathecal onasemnogene abeparvovec be a candidate for managed access?** With limited trial data, an MAA could be an option for further data collection . The SMA Research And Clinical Hub UK (SMA REACH) would certainly collect data and monitor outcomes for research purposes, and as part of global collection of data about treatments for SMA. Lessons must be learnt from the MAA for Nusinersen and Risdiplam where there were data gaps, meaning the data had limited use in the final appraisal process. **Do you consider that the use of intrathecal onasemnogene abeparvovec can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** **1. The "One-and-Done" Factor and its Impact on Daily Life:** A QALY calculation would look at the improved health state over a person's lifetime, regardless of how the treatment is administered. A single, one-time treatment, as intrathecal gene therapy aims to be, is a life-changing benefit in itself. It means an end to the ongoing cycle of hospital visits, painful injections, and constant monitoring that other treatments might require. For a child, this means more time to play, learn etc rather than spending their days as a "patient." For parents, it means a profound reduction in stress, anxiety, and the logistical burden of constant medical care. This emotional and psychological relief is a massive benefit that's hard to quantify. For adults it means more time at work and socialising with the flexibility to enjoy a less medicalised life which our research has shown is a main priority for adults living with SMA. **2. Benefits Beyond Physical Function:**	

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		QALYs typically measure things like mobility, self-care, and usual activities. While these are important, they don't capture the full picture. It isn't just gaining a point on a mobility scale, children and adults are gaining independence and dignity. **-Improved Social Development:** The ability to attend school or work, socialise and participate in family activities. **-Reduced Caregiver Burden:** The profound relief for parents and other family members who can transition from being full-time nurses to being parents and family members. **-Emotional Well-being:** The introduction of new treatments has had a significant, well-documented impact on patients' emotional well-being. This extends to caregivers, who experience joy and relief as their loved ones achieve milestones once thought impossible. The hope for a more stable future, which was previously unimaginable, contributes to a profound but often unmeasured improvement in overall well-being. **3. Preventing Disease Progression vs. Treating Symptoms:** QALY calculations can measure improvements from a baseline, but they may not fully capture the value of preventing a catastrophic decline. The ability of a gene therapy to address the root cause of the disease, rather than just manage its symptoms, is a fundamentally different kind of benefit. It's not just about a better quality of life today; it's about preventing the irreversible loss of motor neurons that would lead to a much worse future. For those diagnosed with SMA, the idea of halting the disease in its tracks is a priceless benefit that goes beyond a simple quality-of-life score. **4. The Value of Hope and Family Well-being:** QALY models generally focus on the individual patient's health outcomes.	

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		The diagnosis of a devastating disease like SMA affects the entire family. The physical and emotional toll on parents, siblings, and extended family is immense. A treatment that offers a real chance of a healthier future provides a benefit to the whole family unit, not just the patient. It allows the family to regain a sense of normalcy and look to the future with hope, rather than fear. This kind of "societal" benefit, which includes the reduced need for informal care and the improved mental health of caregivers, is often difficult to include in standard 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.** SMA UK submissions to NICE and SMC appraisals for SMA treatments to date. Appendix of the joint patient group (SMA UK< Treat SMA/ MDUK) submission for the MAA for nusinersen and risdiplam. SMA REACH PROMS data for the MAA.	
Additional comments on the draft scope	SMA REACH UK	Looking at AEs is a very valid point. Ideally for a period of minimum 3 years, data should be regularly documented and collected on all treatments. Existing registries should be used and supported.	Comments noted.
	Genetic Alliance	We would also recommend that NICE explicitly link evidence requirements with SMA registries and NHS datasets, to ensure systematic collection of long-term outcomes, safety data and patient-reported outcomes. Close alignment with the ongoing nusinersen/risdiplam review will ensure consistency across SMA therapies.	Comments noted.

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

- Neonatal and Paediatric Pharmacists Group