NICE National Institute for Health and Care Excellence

Onasemnogene abeparvovec for treating spinal muscular atrophy

Chair's presentation

3rd Evaluation meeting – post consultation

Highly Specialised Technologies committee, 13th May 2021

Chair: Peter Jackson

Lead team: Paul Arundel, Ron Akehurst, Jeremy Manuel

Technical team: Alan Moore, Nicole Elliott

Company: Novartis Gene Therapies

ERG: BMJ TAG

Onasemnogene abeparvovec (Zolgensma)

Novartis Gene Therapies

Conditional Marketing authorisation	Indicated for the treatment of people: • with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1, or • 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene
Mechanism of action	Gene replacement therapy made of a viral vector modified to contain the primary gene for human survival motor neuron (SMN) protein. When infused, the vector is expected to carry the gene into the nerve cells, enabling production of sufficient amounts of SMN protein
Administration & dose	• Single peripheral intravenous (IV) infusion • Weight based dosing: 1.1 x 1014 vector genome copies per kg (vg/kg) • SmPC gives dosing schedule up to 21 kg
List price and PAS discount	• List price for onasemnogene aberparvovec is £1,795,000 for one-off dose • Simple discount patient access scheme (PAS) approved

NICE SmPC states that there is limited experience in patients 2 years of age and older or with body weight above 13.5 kg. Safety and efficacy in these patients has not been established

Recap - Nature of the condition: Spinal Muscular Atrophy (SMA)

- **SMA type 1 is the most severe form of SMA and the main genetic cause of infant mortality (if untreated)**: symptoms arise before age 6 months. Babies unable to sit independently and have low muscle tone (hypotonia)
- **Affects every aspect of infants life**: never gain developmental milestones after initial presentation, severe muscle weakness affecting movement, swallowing and breathing
- **Severity can be liked to age at which symptoms appear** - earlier onset associated with more severe disease. Time between onset and treatment administration is important
- Most people with SMA type 1 will die before 2 years of age when treated with best supportive care

SMA classification system			
Type	**Age at symptom onset**	**Maximum Motor Function**	**Life Expectancy**
0*	Foetal	Nil	Days to weeks
1	less than 6 months	Never sits	Less than 2 years
2	6 – 18 months	Never walks	20 – 40 years
3	1.5 – 10 years	Walks, regression	As per general population
4*	more than 35 years	Slow decline	

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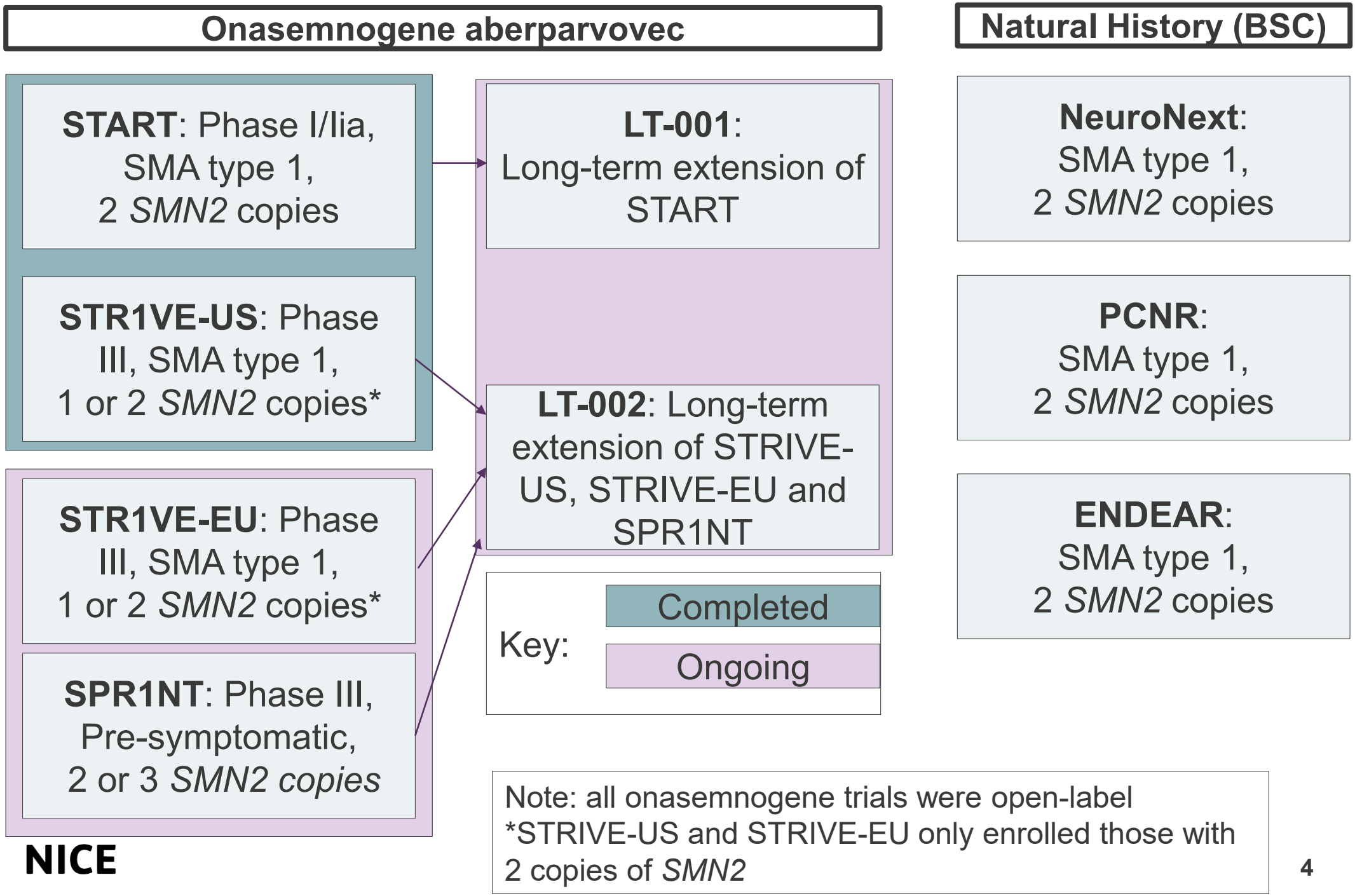
*SMA type 0 and 4 are rarely diagnosed

Recap - Clinical evidence summary



Recap - Summary: START and STRIVE-US

	START	STR1VE-US
Description	Phase I/IIa, open-label, one-time infusion, ascending-dose, single-centre study (US)	Phase III, open label, single-arm, one-time infusion, multi-centre (US)
Trial eligibility criteria	• SMA type 1 with bi-allelic *SMN1* gene mutations with 2 copies of *SMN2* • Patients 6 months of age and younger at date of treatment	• SMA type 1 with bi-allelic *SMN1* gene mutations with 1* or 2 copies of *SMN2* • Patients 6 months of age and younger at date of treatment
Duration of follow up	2 years post dose	18 months of age
Population size	15 (Cohort 1: 3 - low dose. **Cohort 2: 12 therapeutic dose****)	22

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* no patients with 1 copy of *SMN2* enrolled

** Only those receiving therapeutic dose are included in economic analysis

Recap - Summary: STR1VE-EU and SPR1NT

	STR1VE-EU	SPR1NT (Pre-symptomatic)
Description	Phase III, open label, single-arm, single-dose trial	Phase III, open label, single-dose trial
Eligibility Criteria	• SMA type 1 with bi-allelic *SMN1* gene mutations with 1* or 2 copies of *SMN2* • ≤ 6 months of age at treatment	• Pre-symptomatic with bi-allelic deletion of *SMN1*, and 2 or 3 copies of *SMN2* • ≤6 weeks of age at treatment
Selected Outcomes	sitting without support ≥10 seconds	• those with 2 copies *SMN2*, independent sitting ≥ 30 seconds • those with 3 copies *SMN2*, the ability to stand without support for ≥3 seconds
Follow up	18 months	2 copies of *SMN2*: 18 months 3 copies of *SMN2*: 24 months
Population size	33	Currently 30
Completion (estimated)	XXXXXXXX	XXXXXXXXX

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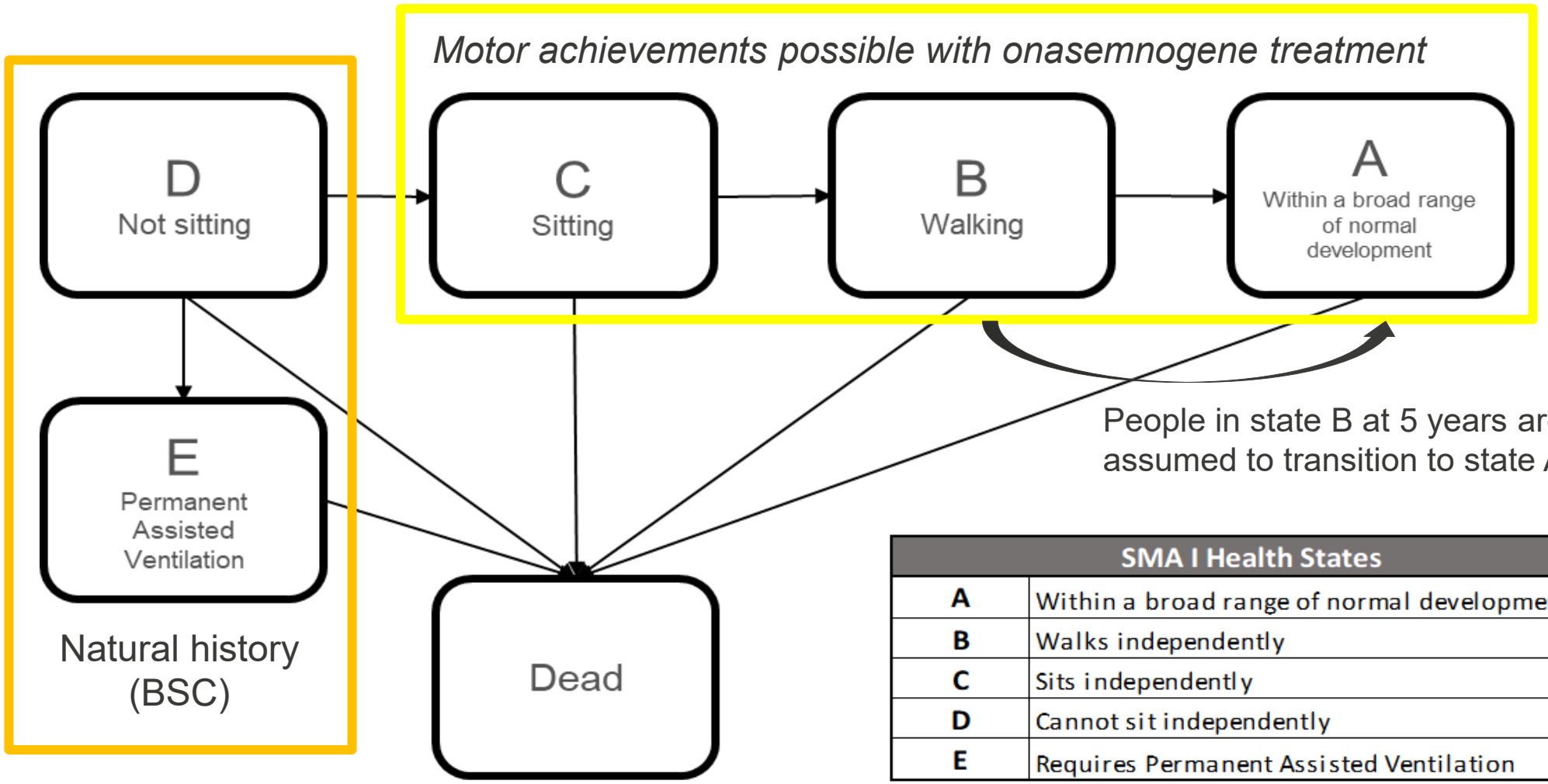
* no patients with 1 copy of *SMN2* enrolled

Company economic model structure



SMA I Health States	
A	Within a broad range of normal development
B	Walks independently
C	Sits independently
D	Cannot sit independently
E	Requires Permanent Assisted Ventilation

Economic model based on motor function and need for permanent assisted ventilation (PAV)

Summary of company and ERG base case assumptions

	Company base case	ERG base case
	Observed pooled data of START (~30 months of age) and STR1VE-US (18 months of age)	
Short term model	Apply an independent sitting threshold of >5 seconds (START) and >30 seconds (STR1VE-US) (state C)	Results for thresholds of >5 seconds and >30 seconds (state C)
	1 additional sitter and 1 additional walker in STR1VE-US assumed between 18 to 30 months (age)	Only observed milestones in base case (1 additional sitter assumed in scenario analysis)
	Motor milestones achieved in first 3 years assumed maintained long term. No milestones gained/lost	

Recap - Cost-effectiveness results overview

Company base case

START and STR1VE-US observed data:

- Offset by 6 months
- 1 additional walker + 1 additional sitter assumed
- Independent sitting >5 seconds for START, >30 seconds for STR1VE-US
- Motor milestones achieved by 3 years are maintained (none gained/lost over time)
- Health state costs = UK HCRU study
- Utilities of 0, 0.19/0.29, 0.65 and general population used for health states E (PAV), D (non-sitting), C (sitting), B/A (walking/normal range of development)
- NeuroNext study informs BSC outcomes

ERG and alternative analysis

- Offset assumption removed*
- Various assumptions (from no additional to 4 additional sitters and 4 additional walkers)***
- Both independent sitting thresholds used in ERG analysis
- Scenario analysis assuming some motor milestone lost*
- US ICER* and TA588 costs** used
- Alternative utility sources used and one-way sensitivity around base case values*
- Alternative natural history studies*

*analysis provided by company, **analysis provided by ERG,
*** analysis provided by both company and ERG

ECD recap: Committee preferred assumptions

The committee considered the following assumptions to be the most appropriate for decision making:

- using the independent sitting threshold of 30 seconds or more
- assuming 1 additional sitter to the observed data from STR1VE US
- applying a 1.5% discount rate for costs and utilities
- assuming that motor milestones gained in the first 3 years in the economic model are maintained in the long term

The committee considered that there was considerable uncertainty associated with the cost-effectiveness analysis of onasemnogene.

To account for these considerable uncertainties, the committee agreed that it would not apply the full QALY weighting of 1.86 but instead would use a lower QALY weighting for its decision making.

ECD recommendations

1.1 Onasemnogene abeparvovec is recommended as an option for treating 5q spinal muscular atrophy (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.

It is only recommended for these groups if:

- permanent ventilation for more than 16 hours per day or tracheostomy is not needed
- the company provides it according to the commercial arrangement (see section 3).

ECD recommendations

1.2 For babies aged 7 to 12 months, the national multidisciplinary team should develop auditable criteria to enable onasemnogene abeparvovec to be allocated to babies in whom treatment will give them at least a 70% chance of being able to sit independently.

1.3 Onasemnogene abeparvovec is recommended as an option for treating presymptomatic 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene in babies, only if the conditions in the managed access agreement are followed.

ECD consultation comments

Consultee comments received from:

- Novartis Gene Therapies
- The Royal College of Pathologists
- SMA REACH UK
- Spinal Muscular Atrophy UK
- Muscular Dystrophy UK

No web comments

ECD consultation comments

Company

- Supportive of recommendations in ECD, including the proposed Managed Access Agreement (MAA) for treatment of pre-symptomatic babies with spinal muscular atrophy (SMA)
    - Acknowledge that trials in the pre-symptomatic population are still ongoing and will supply these completed trial data to inform the MAA as requested
- Provide no additional evidence or analyses

ECD - consultation comments

Broad agreement with the recommendations

Other stakeholders

Comments about implementation (sent to NHSE):

- How the criterion of having a '70% chance of being able to sit independently' is going to be defined/measured/adopted?
- Timing for set up and resourcing of the service.
- Constituency and role of the national multidisciplinary team (MDT).
- Queries about diagnostic testing and reporting.

Comments about groups not covered by the NICE recommendations:

- Babies currently receiving Nusinersin
- Children older than 12 months
- Children with type 2 SMA

Other comments:

Newborn screening programme

Key question

- Is the committee satisfised that no additional considerations are required to the ECD given the responses received from stakeholders?