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

For public – academic in confidence and other confidential information redacted [redacted]

Multiple Technology Appraisal

Technology appraisal committee C [11 November 2025]

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Company: Biogen and Roche

Spinal muscular atrophy (SMA)

SMA is rare, with symptoms and prognosis significantly varying by type

Causes

- Rare, genetic, neuromuscular disorder linked to SMN 1 and 2 genes
- Most common form of SMA is caused by a defect in the SMN1 gene, located on chromosome 5
- Most people with SMA have a related gene called SMN2, the number of SMN2 gene copies a person has can influence the severity of the disease

Epidemiology

- ~70 born with SMA each year, ~1,340 people currently living with it in the UK
- Majority of cases are Type 1 (60%). Types 0 and 4 rarely diagnosed.

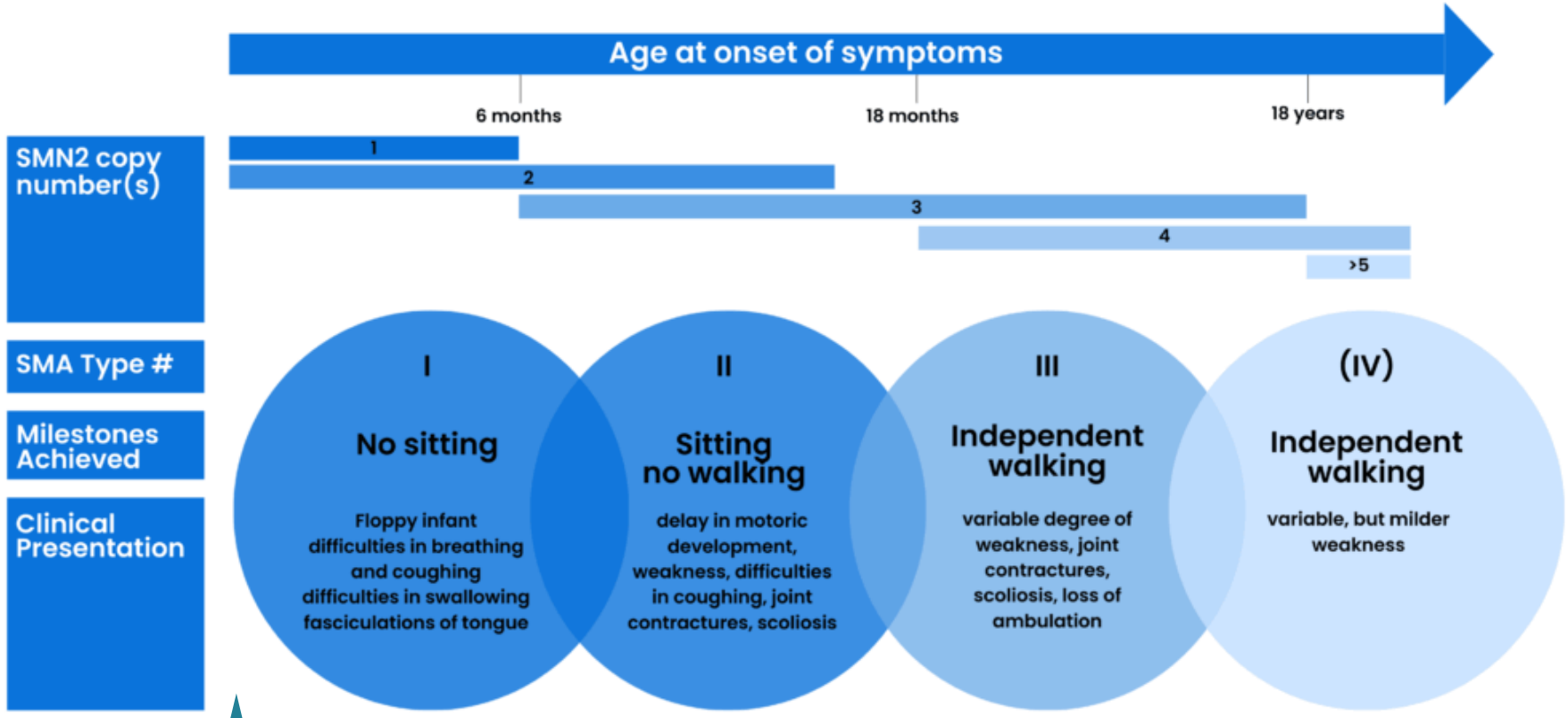
Symptoms and prognosis

- Muscle weakness and progressive loss of movement
- Problems with breathing or swallowing
- Symptom severity and prognosis for untreated SMA varies by type:
  - Type 0: life expectancy of weeks, up to 6 months
  - Type 1: life expectancy up to 2 years
  - Type 2: life expectancy between 30 and 50 years
  - Types 3 & 4: normal life expectancy

SMA = spinal muscular atrophy; SMN = survival motor neuron

Subtypes of SMA

SMA historically categorised by type (according to age of symptoms onset and highest milestone achieved), but types are of decreasing relevance due to genetic testing (SMN2 copy number) and impact of treatment



Schorling et al. (2019). Journal of Neuromuscular Diseases. 7. 1-13.

Additional note: Type 0 SMA presents before birth with reduced or absent foetal movement, and causes profound muscle weakness, respiratory failure, and often congenital heart defects at birth. Typically associated with 1 or 2 SMN2 copies.

TA755/TA588: *The 'SMA type' classification system has limitations but it has been used in the marketing authorisation and/or clinical evidence for interventions*

SMA = spinal muscular atrophy; SMN = survival motor neuron

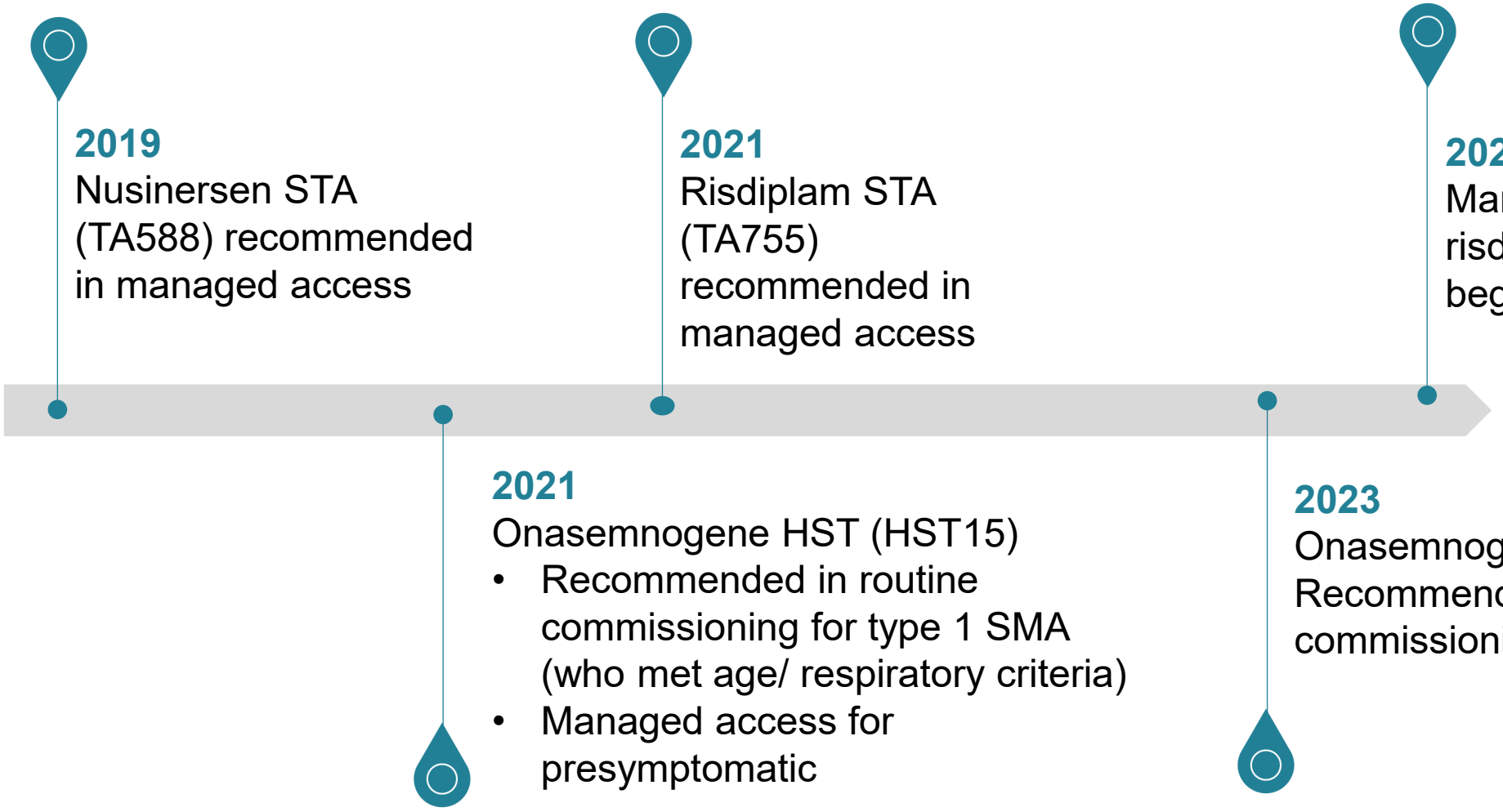
The technologies

Technology	Nusinersen (Spinraza, Biogen)	Risdiplam (Evrysdi, Roche)
Marketing authorisation	Treatment of 5q SMA	Treatment of 5q SMA in patients with a clinical diagnosis of SMA Type 1, 2 or 3 or with 1 to 4 SMN2 copies
Mechanism of action	Modify splicing of SMN2 (a “backup” SMN gene) to increase expression of functional SMN protein	
Drug type	Antisense oligonucleotide	Small molecule
Administration	Intrathecal injection by lumbar puncture • 4 loading doses on days 0, 14, 28 and 63; maintenance dose once every 4 months • 12 mg per administration	Taken orally with oral syringe daily • <2 months of age: 0.15 mg/kg • 2 months to < 2 years of age: 0.20 mg/kg • ≥2 years of age (<20 kg): 0.25 mg/kg • ≥2 years of age (≥20 kg): 5 mg
List price	£75,000 per 12-mg vial of solution for infusion Yr 1 treatment cost: £450,000 Yr2+ annual treatment cost: £225,000	£7,900.00 per 60 mg/80 ml vial of oral solution Estimated annual treatment cost: £240,292 (assumes 5mg dosing based on ≥2 yrs of age [≥20 kg])*
Commercial arrangements	Confidential commercial arrangements are in place (simple PAS discounts)	

* Estimate calculated by tech team for TA755

SMA = spinal muscular atrophy; SMN = survival motor neuron

Topic history



SMA: Managed access agreements

New data comes from pivotal trials, registries and bespoke studies

Table: summary of MAA

	Nusinersen TA588 (2019) Risdiplam TA755 (2021)
Key uncertainties to address	• Long term benefits • Suitability of the model for decision making • Patient and caregiver quality of life • Benefits not captured in the model
Evidence collection	• Ongoing clinical trials • SMA UK and Adult SMA registries • Patient reported outcome research
Other features	• Commercial arrangement to manage risk • Starting and stopping rules • Patient consent

Table: data collected since original TAs

	Biogen (nusinersen)	Roche (risdiplam)
Clinical trials*	• SHINE • NURTURE (pre-symptomatic) • RESPOND (prev. OA) (ENDEAR/CHERISH completed before MAA)	• FIREFISH (T1) • SUNFISH (T2/3) • RAINBOWFISH (pre-symptomatic) • JEWELFISH
Registry data	SMA REACH patient registry data + patient-reported outcomes	
Others		• Patient and carer utility studies • Delphi panel on health state costs

*Length of additional follow-up data included in appendix
Treatment eligibility criteria available in appendix

NICE

MAA = managed access agreement; SMA = spinal muscular atrophy

Decision problem 1

SMA types 0 and 4 are not included in company submissions

	NICE scope	Company submissions
Population	People with types 0, 1, 2, 3 or 4 5q SMA, or pre-symptomatic 5q SMA confirmed with genetic testing with 1 to 4 SMN2 copies	Types 0 and 4 not included
Interventions	Nusinersen and risdiplam	Included
Subgroups	• Number of SMN2 gene copies in people with pre-symptomatic SMA • Functional status (non-sitter, sitter, walker) and baseline motor function and level of motor function • People who have had prior active treatment for SMA • SMA type • By age • By prior treatment (naive or successful) • Patients transition from childhood to adulthood	Analyses split by SMA type: • presymptomatic • type 1 • types 2 & 3 (combined) Biogen included analyses by • No. of SMN2 copies for presymptomatic population • Types 2 & 3 separately Further subgroup analysis limited by lack of data

SMA = spinal muscular atrophy; SMN = survival motor neuron

Decision problem 2

Biogen limits its comparators in each SMA type to only BSC

	NICE scope	Company submissions
Comparators	• Established clinical management • Best supportive care • Nusinersen / risdiplam For children ≤12m with bi-allelic mutation in the SMN1 gene and type 1 5q SMA or pre-symptomatic ≤ 3 copies of SMN2: • Onasemnogene abeparvovec	Biogen only provided analyses of nusinersen vs. BSC for all types. Roche compared risdiplam vs. nusinersen, OA and BSC for presymptomatic and Type 1; vs nusinersen and BSC for Type 2/3
Outcomes	• motor function • bulbar function • frequency and duration of hospitalisation • respiratory function • complications of spinal muscular atrophy • need for non-invasive or invasive ventilation • stamina and fatigue • mortality • adverse effects of treatment • health-related quality of life (for patients and carers)	Roche does not include stamina or fatigue

BSC = best supportive care; OA = onasemnogene abeparvovec

Implications for patients currently having treatment if Final Guidance does not recommend for routine commissioning

MAA for risdiplam states: “existing patients may **continue to receive treatment** until they and their treating clinician consider it appropriate to stop.”

MAA for nusinersen states: “NHS England funding for nusinersen will **cease to be available and treatment will cease** (in which case cessation shall be managed between the marketing authorisation holder and NHS England to ensure it is effected in a controlled manner, this will be agreed in collaboration with the MAA Oversight Committee which includes clinicians and patient groups)”

MAA for risdiplam and nusinersen have been extended until September 2026 meaning access to treatments will be maintained until this time or until NICE publishes final guidance

MAA = managed access agreement

Changes on the horizon

- **Newborn Screening:** UK National Screening Committee is working with the SMA Partnership Board to evaluate the feasibility of newborn screening for SMA; evaluation still being scoped, final decisions pending
- **SMA Care UK Project:** A 3-year initiative led by clinicians and patient groups aims to update and implement UK Standards of Care for SMA. Focus areas include:
  - Bone health
  - Hip management
  - Respiratory care
  - Spine management
  - Transition to adult care
- **New treatment modalities/options:**
  - New formulation of risdiplam approved by MHRA in July 25: tablet that can be swallowed whole or dispersed in water (for patients ≥ 2 years of age with ≥ 20 kg)
  - DEVOTE trial suggests higher dose nusinersen (50/28 mg) may offer benefits vs. standard 12mg dose
  - OA is a one-time intravenous gene therapy for children under 2 years or weighing <21 kg, but new intrathecal formulation is being developed for older and heavier patients (STEER trial)

OA = onasemnogene abeparvovec

Treatment options

Based on NICE recommendations

Routine commissioning | Managed access

SMA Types					
Presymptomatic with 1 to 4 SMN2 copies. Found by targeted testing of related individuals	1	2	3	4	0

- Onasemnogene (<12m)* → *May not be suitable for people with high AAV9 antibodies*
- Nusinersen → *Intrathecal injection; may not be suitable for people with severe scoliosis or spinal fusion*
- Risdiplam → *Not suitable if trying to conceive, or pregnant/ breastfeeding*
- Best supportive care

People having permanent ventilation are typically not eligible for these treatments

- In addition to treatment, people have multidisciplinary supportive care including nutritional support, respiratory support, physiotherapy, assistive technologies, occupational therapy and social care.

Which comparators are appropriate for each population?
What proportion of SMA patients cannot be treated with nusinersen due to lack of access to spinal canal?

* 1) Presymptomatic with bi-allelic SMN1 mutation and up to 3 copies of SMN2 gene in babies <12m, (HST24)
2) type 1 diagnosis, aged <6m, or 7-12m if agreed by national multidisciplinary panel (HST15)
3) >12 months, or having treatment with nusinersen and risdiplam, but in scope of EMA marketing authorisation and if agreed by national multidisciplinary panel (NHSE agreement)

Overview of stakeholder submissions

Submissions received from:

- 3 patient experts
- 3 patient organisations (joint submission from Spinal Muscular Atrophy UK, Muscular Dystrophy UK
- and Treat SMA)
- 1 clinical expert
- NHS England
- 3 professional organisations:
  - SMA Reach UK
  - Adult SMA Reach
  - Association of British Neurologists

Organisations who provided consultation comments on the EAG report included:

- SMA Reach UK
- Adult SMA Reach
- Association of British Neurologists
- Novartis (manufacturer of onasemnogene)
- Combined response from:
  - Spinal Muscular Atrophy UK
  - Muscular Dystrophy UK
  - Treat SMA

Patient perspectives on living with SMA

- Progressive decline: ongoing loss of strength and mobility; risk of serious respiratory illness
- Mental health impact: uncertainty about future loss creates anxiety, continuous grieving and chronic sorrow
- Small functional differences matter: movement in a finger, can have an enormous impact on quality of life, enabling work and independence (e.g., wheelchair or computer use)
- Speech Challenges: reduced articulation and volume affect school and employment
- Loss of function can lead to social isolation, such as avoiding socialising once ability to eat or drink is lost
- Delays in diagnosis, and inequities in care and management exist across the UK
- Getting the necessary equipment and support (e.g. physio) to maximise independence can be a struggle and often people self-fund/fundraise for this

"If I lost the ability to use a mouse there's a good chance I'd also lose my ability to do my job. As the sole bread winner within my family this would have a catastrophic impact. These are the details that people don't understand."

"I have a constant "sword of Damocles" hanging over my head as to what function I am going to lose next, all of which has an indescribable impact on my mental health."

Further detail on patient perspectives provided in qualitative analysis of registry data – see here

Impact on carers and family

Caring for someone with SMA impacts the wider family in several ways:

- Caring for someone with SMA is extremely consuming, given extensive, complex, round-the-clock needs
- Carers health and wellbeing suffers due to the physical and emotional demands of being a carer; stress, anxiety, back pain etc.
- Inability to work due to caring responsibilities
- Carers have less time and attention for siblings and their needs
- Financial implications due to costs of self-funding additional support and equipment, and reduced ability to work
- Restrictions on family activities (e.g. days out and holidays) and socialising (such as parties and sleepovers etc)
- Lack of social care and mental health support for families

"My son's physical needs consisted of dressing, toileting, bathing, washing, assisting with meals and snacks throughout the day, getting [name] anything he needed, changing his position throughout the day from the floor, to wheelchairs or turning him throughout the night. Ultimately, being there to assist him 24/7"

"It is very difficult to spend any quality time with my husband as one of us must always be in the house with the nurse to fulfil the conditions of his care package."

"My health issues always come second, as my children will always come first"

"[My son] also has a sister, 11 months older...I had immense feelings of guilt as I had to prioritise him"

Further detail on patient perspectives provided in qualitative analysis of registry data – see here

Impact of treatment

People report the following benefits from treatment, which have led to improved quality of life:

- Improved strength, stamina, lung capacity, mobility
- Less severe respiratory infections and fewer hospital admissions
- New functions gained and/or existing functions sustained
- Improved education and work attendance, volume and diction of voice; positive impact on socialisation for people with SMA and carers
- Reduced anxiety about choking and loss of function, hope for the future
- Improved mental health for carers due to hope for the future, less stress and worry due to improved physical health and independence of the person living with SMA

They also noted that:

- Side effects and inconvenience of treatment are manageable and justifiable given the treatment benefits
- Even if there is no improvement, being able to maintain existing abilities (stabilisation) is extremely valuable
- Physiotherapy assessments don't capture holistic picture of improvements and their impact on patient & family quality of life, such as bulbar function, stamina and fatigue

"I can eat and drink without worrying about of choking and no longer have to consider the thought of dying each time I sit down for a meal."

"[My son] is now 7 and since he was 3, he has not had any more admissions to hospital."

"I was told I probably wouldn't live beyond 40…Treatment has given me hope that while I may not live to 100, there is now no predefined expiry date that I am living to."

"My son's school attendance has risen from 27% to 98% and he is now one of the top students in his class."

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Further detail on patient perspectives provided in qualitative analysis of registry data – see here

Clinical expert and professional organisations perspectives

Benefits of treatment :

- Treatments have clinically meaningful benefit, slowing progressive decline in motor, respiratory and bulbar function
- This reduces hospital admissions, improves independence; improves speech and enables school attendance/proper education as well as work attendance
- Benefits seen in both clinical trials and RWE
- For progressive disease like SMA, stopping/slowing the decline is important treatment outcome. Stability is a benefit.
- In addition to stopping/slowing progression, some patients achieve new milestones and improvements
- Preserving ability to move fingers has meant the difference between operating a powered wheelchair/computer or not
- Patients report functional benefits and QoL improvements which are not captured by existing scales
- Treatments have greatest benefit in pre-symptomatic cases (diagnosed via newborn screening)

"As long as SMA is diagnosed through symptoms rather than routine screening, there will be significant unmet need"

"Ventilated patients are excluded from treatment currently, but being long term ventilated does not necessarily mean someone cannot have some independence…Should be more room for clinician discretion."

"These 2 therapies have dramatically changed the way SMA progresses to the point that some of the classical descriptions do not apply any more, especially for treatments initiated early"

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RWE = real world evidence; QoL = quality of life

Treatment choice

Stakeholders noted the differences between treatment options, emphasising that choice is crucial

- Previously, spinal fusion surgery didn't preserve access to the lumbar area (no treatment available, so not needed). So nusinersen isn't a practical treatment for many people, particularly aged 25+.
- For nusinersen, some people may need a robust support network to help with hospital visits. But on the plus side, you don't need to think about treatment between visits, which some prefer over daily doses
- Risdiplam can be taken at home, is easily stored and provides the flexibility for people to travel
- With nusinersen, clinician is assured that treatment has been administered (useful if safeguarding concerns)
- Useful to have option to switch treatments due to side effects, contraindications or no/poor response (inc. after gene therapy). But don't want to be forced into this; some may be reluctant to switch due to the fear of an irreversible loss in function if they don't respond well to the other treatment
- Nusinersen/risdiplam have less rigorous post-treatment monitoring than gene therapy, and the family doesn't need to shield for extended periods due to immunosuppression
- Important to have access to nusinersen and risdiplam as bridge therapies; can start quickly while waiting for gene therapy. Increasingly important if newborn screening introduced

Clinical expert: 'It is vital to keep all three treatment options given contraindications/ adverse events'

"Circumstances where there may be a need for … flexibility include pregnancy and breastfeeding (coming off risdiplam); degree of disability… levels of ambulation…."

EAG qualitative analysis – clinical

EAG conducted thematic analysis to provide qualitative insights from multiple sources:

- Meetings with professional and patient organisations, arranged by NICE
- Submissions from patient and professional organisations, patient and professional experts
- Case studies and quotations shared by SMA UK, Muscular Dystrophy UK and SMA Reach
- Free-text data for adult and paediatric populations provided to the EAG by SMA REACH UK

Impact on socialising

- Isolation and reduced social interaction are common among people with SMA and their carers
- Carers experience significant social and relational strain, with many reporting changes or breakdowns in intimate relationships and friendships due to caregiving responsibilities
- Nusinersen and risdiplam have enabled better social engagement and reduced isolation

Function, independence, and quality of life

- Difficulties with eating, toileting, and mobility, often requiring full-time care and assistive equipment
- Stabilisation of condition is highly valued, with patients and carers reporting that even maintaining current function significantly enhances independence and mental wellbeing
- QoL improves with increased independence, reduced fatigue, education, work, and hobbies

Systemic challenges and the need for choice

- Treatment access is unequal, with those with Type 4 SMA or on long term ventilation facing more barriers
- Patient choice is critical, as responses to treatments vary widely; having multiple options is crucial

EAG = evidence assessment group; QoL = quality of life

EAG qualitative analysis – economic

Financial burden and out-of-pocket costs

- Families affected by SMA often face substantial financial pressures due to limited NHS coverage for essential services and equipment
- Many resort to private therapies, fundraising, and personal purchases of specialist items like modified wheelchairs and hydrotherapy tools to maintain quality of life and independence

Inequities in access to care

- Submissions highlighted significant disparities in service availability across regions and between age groups
- Adults with SMA often experience fragmented care pathways and limited access to services such as orthotics, physiotherapy, and social care, leading to reliance on family support or private alternatives

Treatment administration

- Experts noted that the broader economic impacts—especially private costs and informal care—are difficult to capture in standard metrics like QALYs, complicating health technology assessments

Selected quotes from patient and clinical experts are available in supplementary appendix

EAG = evidence assessment group; QALY = quality adjusted life-year

Starting/Stopping criteria

Current MAAs include starting and stopping rules

Starting rules include:

- People do not receive medicines in combination
- People must not have had successful treatment with onasemnogene abeparvovec
- People must not be on permanent ventilation

Stopping rules include:

- People have a diagnosis of an additional progressive, life-limiting condition such as terminal cancer or catastrophic brain injury
- Persons condition showing a lack of benefit from treatment, defined by worsening motor function and requirement for permanent ventilation

See managed access arrangements for nusinersen and risdiplam for full details

Detailed stopping rules are available in appendix

Are the starting/stopping rules from MAA appropriate for routine commissioning?

MAA = managed access agreement

Equality issues and groups without access

Disability

- Clinical expert: Excluding people who need long term ventilation may be an equality issue.
- NHSE: challenging to assess benefit in severely disabled people. Fine motor skills not well captured in tools.

Age

- Patient expert: If risdiplam were not recommended, this would remove available treatment for those who have spinal fusions. This disproportionately affects people for whom surgery didn't maintain spinal access
  - people over the age of 25 to 30 are more likely to have spinal fusions, would not have equal access
- NHSE: challenges monitoring benefit in a patient who is growing (children and young adults)

Access for types 0 & 4

- Type 0 classification is not based on any biomarker and depends on the diagnosing clinician
- ABN says pragmatic extrapolation to other subtypes, particularly type 4, should be considered
  - they are currently excluded from treatment (see slide 36)
  - NHSE says ~10 people with type 4 SMA have no treatment access in England

Treatment choice

- Access and availability of routine treatments and best supportive care varies significantly across the country
- Treatments have different contraindications, crucial that all 3 options are available (e.g. family planning).

Why do some SMA groups not currently have access to treatments?
Are there any equality implications to consider in relation to these groups?
Are there any other equality issues not captured here?

ABN = Association of British Neurologists; NHSE = NHS England

Key issues

Issue	ICER impact
Clinical effectiveness	
Decision-making comparator	Large
Sensitivity of motor function assessment tools	Large
Lack of data for type 0 or 4 SMA	Unknown
Cost-effectiveness	
Functional changes captured in utility values	Large
Utilities for severe health states	Large
Carer quality of life	Large
Treatment discontinuation	Unknown
Costs for severe health states	Large
High background care costs	Large
Severity modifier for presymptomatic and type 2/3 populations	Large

Clinical effectiveness

Presymptomatic SMA pivotal trial results (efficacy)

Nusinersen and risdiplam improve milestones and survival

Nusinersen (NURTURE)*	Risdiplam (RAINBOWFISH)
At ~5 yrs treatment: • 100% children were alive and without permanent ventilation (16% required respiratory intervention) • 100% children achieved sitting without support (WHO) • 92% children were able to walk alone (WHO) • 88% reached the maximum CHOP INTEND score • No motor skills were lost during observation period At 8-yr exploratory data: • 100% were alive and without permanent ventilation • 100% children with 3 *SMN2* copies achieved all 6 WHO motor milestones • 87% with 2 *SMN2 copies achieved* walking alone	At 1 year of treatment (ITT population), • 100% children were alive and without permanent ventilation • 96% children able to sit without support (HINE-2), • 52% children able to stand unaided, 32% aided (HINE-2) • 48% children able to walk independently (HINE-2) At 2-year exploratory data, • 100% of infants were able to sit without support (HINE-2) • 87% of infants were able to walk independently (HINE-2)

- The studies showed that presymptomatic treatment helps children with SMA achieve major motor milestones (such as standing and walking), often at rates consistent with normal development

* Infants with 2 or 3 copies of SMN2 (most likely to develop Type 1 or 2)
± Infants had 2 or more SMN2 copies. One infant with ≥4 SMN2 copies could not be assessed

For trial designs see appendix
For details of outcome measures see appendix

Type 1 SMA pivotal trial results (efficacy)

Nusinersen and risdiplam improve milestones and survival

Nusinersen (ENDEAR)	Risdiplam (FIREFISH)
After 13 months treatment: • 51% of children in the nusinersen group were motor milestone responders vs. 0% for control • 47% reduction in risk of mortality or permanent ventilation vs. control (HR: 0.53, p = 0.0041) • 34% reduction in risk of permanent ventilation vs. control (HR: 0.66, p = 0.1329) ENDEAR/SHINE± (extension study). At [redacted] yrs follow-up • [redacted] on nusinersen died or required permanent ventilation vs [redacted] for previous control • [redacted] of children in previous nusinersen group could sit without support, vs [redacted]% in previous control (WHO) • [redacted]% of children in previous nusinersen group could walk with assistance, vs [redacted]% in prev. control (WHO)	After 1yrs of treatment (Part 2 study): • 85.4% of children were alive and without permanent ventilation • 78.0% classified as motor milestone responders vs 12% expected natural history (HINE-2) After 2yrs of treatment (Part 2 study): • 43.9% of children could sit without support for 30s (BSID-III) • 0% were able to stand or walk alone (BSID-III) • 90.2% had increase CHOP-INTEND score by ≥ 4 pts After 5 years of treatment (Part 2) • [redacted]% were sitting without support for 30 seconds (BSID-III) • [redacted]% were able to stand alone (BSID-III)

In contrast to the milestones achieved in the trials, untreated patients would never sit without support, and only 25% would survive beyond 14 months.

± In SHINE extension, all participants who were previously in control arm received nusinersen. HR = hazard ratio

For trial designs see supplementary appendix
For details of outcome measures see appendix

Type 2/3 SMA pivotal trial results (efficacy)

Nusinersen and risdiplam improve motor function and upper limb function vs control

Nusinersen (CHERISH)	Risdiplam (SUNFISH)

At month 15:
• Change in HFMSE: +3.9 for nusinersen vs -1.0 for control
• Motor milestone: 19.7% achieved new motor milestones compared to 5.9% with control (WHO)
• Response (≥+3 points in HFMSE): 56.8% for nusinersen vs 26.3% for control
• Change in RULM: +4.2 for nusinsersen vs +0.5 for control
• CHERISH/SHINE± (extension, ~[redacted]yrs):
  • mean no. new motor milestones: [redacted] for prev. nusinersen vs[redacted]for prev. control
  • Mean total HFSME score: [redacted]for prev. control vs[redacted]points for prev. nusinersen
  • RULM score: [redacted]points in prev. control patients vs [redacted]points in prev. nusinersen
	At 1yr of treatment,
	• Motor function: 1.36-point increase in MFM-32 for risdiplam group, vs 0.19 decrease with placebo.
	• Upper limb function: 1.61 increase in RULM score for risdiplam group vs 0.02 increase with placebo
	
	Treatment for [redacted](open label extension) resulted in [redacted] in motor function (MFM32), and [redacted]of upper-limb function (RULM)*
	• MFM32: mean change -[redacted]% and [redacted]% had a change of ≥0 and ≥3
	• RULM: mean change [redacted]% and [redacted]% had a change of ≥0 and ≥2
	• HFMSE: mean change [redacted]% and [redacted]% had a change of ≥0 and ≥2

* No control for extension study

± In SHINE extension, all participants who were previously in control arm received nusinersen. HR = hazard ratio

For trial designs see supplementary appendix

For details of outcome measures see appendix

Indirect treatment comparisons

Companies conducted ITCs due to lack of direct comparative data

Background:

- Nusinersen and risdiplam populations are different within MAAs and trials as nusinersen available first
- Historically, people taking risdiplam more severe vs those treated with nusinersen
- Risdiplam early access scheme was for people ineligible/unsuitable for other treatments i.e. nusinersen
- Both companies said the results of ITC had considerable uncertainty
- Roche says some are suitable for decision making in Type 1 and Type 2/3 SMA, Biogen says they are not

Biogen

- 14 analyses were conducted, including 12 MAICs and two STCs; none have been used in models
- Comparisons had high risk of bias due to lack of randomisation and comparisons beyond observed data
- Heterogeneity in patient characteristics, treatments, and outcome timepoints undermined comparability
- Inconsistent outcomes and misaligned milestone definitions required assumptions that lacked clinical validity
- Small effective sample sizes and poor covariate overlap limited the reliability and interpretability of results

Roche

- **Presymptomatic SMA:** MAICs/STCs not feasible, naïve comparison performed. Comparisons are highly uncertain and 'uninformative' due to very small sample sizes, baseline differences, inconsistent assessment schedules, and motor milestone reporting; not used in modelling (assume equal efficacy).

ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; MAA = managed access agreement; STC = simulated treatment comparison

Indirect treatment comparisons

Are the ITCs suitable for decision making?

Companies conducted ITCs due to lack of direct comparative data

Roche (cont.)

- **Type 1 SMA:** ITC accepted in TA755 used for BSC. For OA, transition probabilities have based on the unanchored MAIC conducted on the BSID-III endpoint, despite high uncertainty. For nusinersen, transitions are based on HINE-2 MAIC, chosen to avoid overfitting and to minimise bias
- **Type 2/3 SMA:** odds ratio for the RULM MAIC between risdiplam and nusinersen used in base case, comparisons face reduced effective sample sizes and substantial uncertainty in endpoint estimates post-12 months, limiting the ability to draw conclusions, however the measure was used due to clinical expert opinion that RULM is more informative than HFMSE

EAG

- Clear attempts made by both companies to make the analyses possible and plausible with available data
- Concerns about comparability of the different cohorts, where effective sample sizes are low after matching
- Sample size concerns mainly driven by availability of data in a rare disease
- Concern with comparability of placebo and sham arms for anchored Roche MAIC in type 2/3
- Biogen type 2/3 analysis is based on STC; given inherent differences between the populations, not running an anchored MAIC may make sense clinically
- Quality of data available from ITCs restricted EAG's ability to assess relative effectiveness of DMTs

Results of Biogen and Roche ITCs summarised in tables 6.3 and 7.4 of EAG report (respectively).

BSC = best supportive care; DMT = disease-modifying therapy; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; OA = onasemnogene abeparvovec; STC = simulated treatment comparison

Key Issue: Decision-making comparator

Stakeholders disagree on whether nusinersen and risdiplam can be compared directly

Background

- **TA588:** BSC is appropriate comparator as nusinersen was first DMT for SMA
- **TA755:** BSC appropriate comparator because nusinersen only available in managed access, HST24 not yet published, and treatment switching between DMTs would only be in exceptional circumstances

Table: comparators used in current company and EAG base cases, exploratory comparators in brackets

SMA Type	Biogen	EAG-Biogen	Roche	EAG-Roche
Presymptomatic	**BSC**	**BSC (*OA*)**	**Nusinersen*, OA* (*BSC*)**	**BSC (*Nusinersen, OA*)**
Type 1	**BSC**	**BSC (*OA*)**	**Nusinersen, OA (*BSC*)**	**BSC (*Nusinersen, OA*)**
Type 2/3	**BSC**	**BSC**	**Nusinersen (*BSC*)**	**BSC (*Nusinersen*)**

Roche

- Expert opinion and market research shows <5% of people would have BSC in the UK, it is more appropriate for a comparison to treatments that reflect the true proportion of care in the NHS
- Comparison vs BSC lacks validity, goes against the spirit of the MTA process, and does not solve the underlying issues associated with differences in trial populations
- Understand that BSC is easier to model, but this reason alone is insufficient

*Assumes equivalent efficacy for all interventions

BSC = best supportive care; OA = onasemnogene abeparvovec; MTA = multiple technology appraisal;

Key Issue: Decision-making comparator

Stakeholders disagree on whether nusinersen and risdiplam can be compared directly

Biogen

- Comparisons against BSC do not reflect UK practice, but BSC comparison is more appropriate use of available data without further complexity and uncertainty

EAG

- EAG base case uses Biogen models for nusinersen vs BSC, and Roche models for risdiplam vs BSC
- This is to avoid biases due to differences in nusinersen and risdiplam populations in the data submitted

Stakeholders

ABN, (Adult) SMA Reach: meaningful comparison between nusinersen and risdiplam is not possible due to differences in patient populations and treatment timing, a direct comparison would not be fair
Novartis: OA is established in UK for presymptomatic and type 1 SMA, OA should be considered a comparator
SMA UK+: BSC is rarely delivered in full so the model over-estimates outcomes for the comparator arm

ICER report*:* insufficient data to estimate and compare net health benefits of risdiplam, nusinersen, and OA
SMC report: substantial differences between studies and difficult outcomes to measure, the results of the comparison between interventions are uncertain; equal effectiveness assumed for nusinersen and risdiplam

Given data limitations, which comparators can be considered for each population?
Should BSC followed by symptomatic treatment be a comparator for presymptomatic population?

BSC = best supportive care; OA = onasemnogene abeparvovec;

Summary of MAA registry data

Registry data showed treatment led to maintaining or gaining of motor milestones

- Data on ~400 children and ~400 adults with SMA collected from 17 centres across England

Follow up:

- Paeds; nusinersen had longer follow-up than risdiplam for motor outcomes (~4+ yrs vs ~1.5+ yrs)
- Adult; ~4 yrs follow-up data for both treatments, but fewer people at this point for risdiplam than nusinersen

Results:

- Both the nusinersen and risdiplam MAAs separately suggested maintenance or improvement, mostly for motor outcomes, across all SMA types assessed
- Quantitative data for patient-reported outcome measures was lacking for both treatments and suggested mixed results. Data surrounding QoL were also lacking but did suggest some improvement.

Use of registry data in modelling:

- Biogen: Treatment discontinuation data used in base case. Limited additional use of quantitative data due to patients having longer disease duration and higher symptom burden than expected future real world patients
- Roche: Proportion of people having treatment at home from MAA used in base case, and baseline characteristics used in scenario. Limited additional use of quantitative data due to short term follow up and higher baseline severity than expected future real world patients

MAA = managed access agreement; QoL = quality of life;

Adult registry results

Nusinersen and risdiplam lead to maintaining or gaining of motor milestones

	Nusinersen (n=[redacted])	Risdiplam (n=[redacted])
WHO Motor Milestones	• [redacted] • [redacted] • [redacted]	• [redacted] • [redacted] • [redacted]
Functional scores	• [redacted] • [redacted] • [redacted]	• [redacted] • [redacted] • [redacted]
Survival	[redacted]	[redacted]
Perm. ventilation	[redacted]	[redacted]
Discontinuation	[redacted]	[redacted]
Follow up	[redacted]	[redacted]

For summary of data collected see supplementary appendix

Paediatric registry results

Nusinersen and risdiplam lead to maintaining or gaining of motor milestones

	Nusinersen (n=[redacted])	Risdiplam (n=[redacted])
Motor function	• [redacted] • [redacted] • [redacted]	• [redacted] • [redacted] • [redacted]
Survival	• [redacted] • [redacted] • [redacted]	• [redacted] • [redacted] • [redacted]
Ventilation	[redacted]	[redacted]
Discontinuation	[redacted]	[redacted]
Follow up	[redacted]	[redacted]

For summary of data collected see supplementary appendix

Key Issue: Sensitivity and relevance of assessment tools

Assessment tools used in trials don't capture all aspects of SMA, and aren't sensitive enough

Background

- **TA588**: motor function not the only factor affecting health-related quality of life; factors such as respiratory function, pain and physical impairment also important outcomes for people with SMA
- **TA755**: small improvements in motor skills are highly valued by patients and make a large difference to QoL, which may not be captured in the available motor function measures

Roche

- Experts say mobility is not the entire condition, unsure if stratifying QoL by motor function is appropriate
- During managed access, made extensive efforts to generate additional data on health related QoL
- Conducted a utility study in people with SMA and their carers, but unfortunately had data limitations
- SMA community is passionate about the importance of disease-related complications (such as scoliosis, respiratory support and bulbar function) on quality of life, capturing these in the model is covered here

Biogen

- Considered including interim milestones for more granular outcomes but this would have involved substantially higher number of data gaps
- Experts noted that people on active treatment are likely to obtain functional benefits that are uncaptured with gross motor milestones, such as those "sitting without support" gaining additional upper limb function

QoL = quality of life;

Key Issue: Sensitivity and relevance of assessment tools

Assessment tools used in trials don't capture all aspects of SMA, and aren't sensitive enough

Stakeholders

ABN: outcome measures are insensitive to detect meaningful functional change, especially bulbar function, also small changes in upper limb and hand function can have a profound impact on quality of life

Adult SMA Reach: in some instances, it is difficult to capture benefit in a consistent way, e.g., outcome measures for stamina, fatigue or bulbar function have not yet been implemented

SMA Reach: lack of data on bulbar function, stamina, fatigue, education, daily care and SMA burden

SMA UK+: a "small" change in a clinical score can equal a monumental improvement in daily life – the ability to independently operate a wheelchair, lift a hand to eat, or even maintain current function rather than decline

EAG

- Motor function tools lack granularity to capture changes that patients, carers, clinicians consider important
- There is focus on gross motor skills (e.g. crawling, sitting), whereas fine motor skills (e.g. wheelchair control) are not captured and these are considered crucial skills to be maintained by patients, carers and families
- EAG assumed utility and costs of bulbar function, non-ventilatory respiratory support and scoliosis are already captured, did not add to avoid double counting with health state utility values and resource costs
- Stamina and fatigue also identified as important to patients, but EAG found some limited data

How does this link with the economic analysis (see here)?
Are relevant functional changes captured in the economic evaluation?

Key Issue: Lack of data for Type 0 or Type 4 SMA

Stakeholders are concerned about equity of treatment access for people with type 0 & type 4 SMA

Background

- SMA can be grouped into 5 main types (0 to 4), but main evidence submitted is for SMA types 1 to 3
- Nusinersen's marketing authorisation would allow treatment of types 0 and 4, risdiplam's would not
- Type 0 and 4 SMA are rarely diagnosed in clinical practice in the NHS in England

Biogen

- Acknowledge limited data for nusinersen in type 4 SMA is insufficient for health technology appraisal
- However, excluding type 4 patients from a recommendation may widen health inequalities for SMA patients

Stakeholders

- **ABN:** concerned about equity of treatment access across SMA types, categorisation into types 0–4 is arbitrary because underlying genetic pathology is the same across subtypes – adults with type 4 SMA have biological plausibility that they could benefit from increased SMN protein levels but cannot have treatment
- **Adult SMA REACH:** unmet need for type 4 SMA, people would benefit from accessing nusinersen, estimate the cohort is currently 10-15 patients in UK
- **SMA REACH:** significant data limitations for type 0 SMA, there are a few international cases available
- **SMA UK+:** advanced diagnostics means clinical typing in SMA is outdated, SMA is a spectrum with arbitrary cut offs – urge NICE to consider the ethical implications of denying access

NICE

How can the lack of data for Types 0 and 4 SMA be considered in decision making?

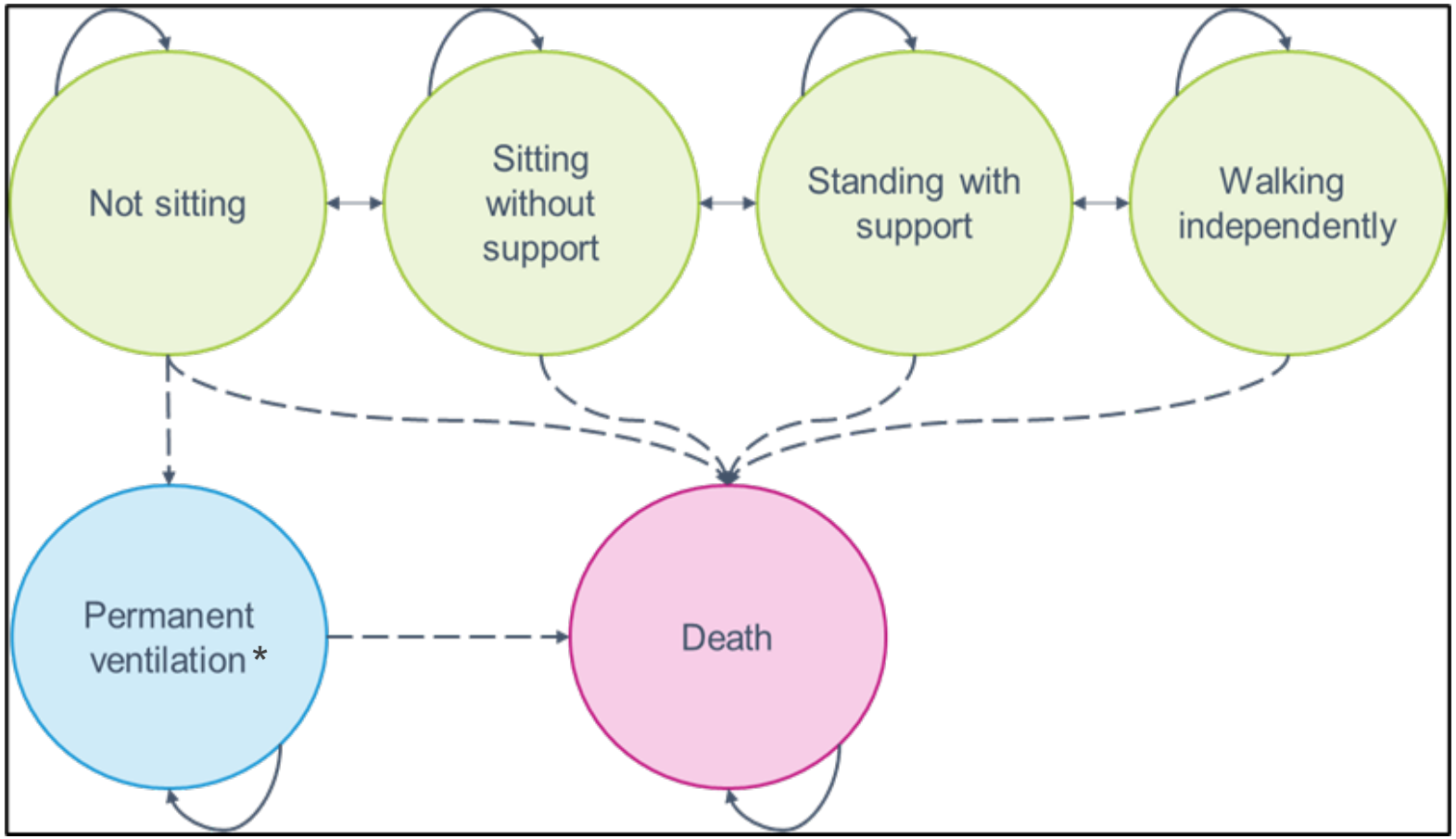
Cost-effectiveness

NICE National Institute for Health and Care Excellence

Model structures

Both companies use Markov model structures with different health states

Example of model structure (*Biogen type 1 model*)



* used in presymptomatic and type 1 SMA models only

- People in the model could move between all health states multiple times apart from death and permanent ventilation states (when used in model)
- The EAG models were adapted versions of the Roche models (for risdiplam) and Biogen models (for nusinersen)
- Time horizons:
  - [redacted] years (Roche)
  - 100 years (Biogen)
- Cycle length:
  - 4 months (Biogen)
  - 1 month (Roche)
- Discount rates: 3.5%

Health states used in the models

Presymptomatic / Type 1 SMA

Roche	Motor scale	Biogen	Motor scale
Permanent ventilation	N/A	Permanent ventilation	N/A
Non sitting	HINE-2	Not sitting	• Presymptomatic: WHO motor milestones • Type 1: HINE-2 for < 2yrs, then WHO for 2yrs+; assumed equivalence despite different definitions
Sitting		Sitting **without** support	
Standing		Standing **with** support	
Walking		Walking **independently**	

Type 2 / 3 SMA

Roche	Motor scale	Biogen	Motor scale
Non sitting	MFM-32	Not sitting	
Sitting **without** support		Sitting **without** support	WHO motor milestone
Sitting **with** support			
Standing		Standing **with** support	
Walking	HMFSE	Walking **independently**	

The number of people starting the model in each health state differed by SMA type and intervention model
See key issue around whether functional changes are accurately captured in the model

Company and EAG base cases

EAG base case used adapted versions of the company base cases

- EAG made edits to company base case models to produce EAG base case models
- EAG made limited changes to the Biogen base case for nusinersen, but made more changes to the Roche models for risdiplam
- Differences across Roche and Biogen models included (key differences are key issues):
  - Time horizon
  - Treatment effect duration
  - Survival
  - Treatment discontinuation
  - Utility values for patients and carers
  - Adverse events
  - Health state costs
- See the supplementary appendix for further details of EAG and company base case differences

What assumptions and inputs for the Biogen and Roche models would be expected to be the same?

Key Issue: Functional changes captured in utility values

Utility values may not fully capture disease changes that are meaningful

Background

- **TA588:** Utilities may not capture added benefits of gaining particular motor skills. But data presented did not suggest that there were distinct and substantial benefits not captured
- **TA755:** company increased utility by 0.2 for sitting / non-sitting states, and by 0.05 for carers, and used disutility for scoliosis, respiratory and bulbar function – committee concluded health state values were implausible

Biogen

- Base case included on-treatment utility increment of 0.1 (clinical expert opinion) for nusinersen to allow for gains in quality of life (such as upper limb function) that were not captured in the health state utility values

EAG

- EAG base case models included 10% utility increment to account for uncaptured nuanced improvements
- EAG base case assumed utility and costs of bulbar function, non-ventilatory respiratory support and scoliosis are already captured in utility values and costs, did not add again to avoid double counting
- Explored in scenario by including utility decrement and extra healthcare costs for bulbar function in type 2/3 model as experts highlighted the importance of this, but analysis is limited due to data and assumptions
- Not possible to model this for presymptomatic or type 1 populations due to a lack of relevant data
- Stamina and fatigue also identified as important to patients, but EAG could not find data it could use

Key Issue: Functional changes captured in utility values

Utility values may not fully capture disease changes that are meaningful

Roche

- Accept 10% utility increment for nuanced motor improvements, but consider it arbitrary and may not adequately capture all minor motor benefits
- Disappointed EAG has not adopted Roche's efforts to capture disease-related complications as in Roche submission, heard from patients these are very important
- Disutility for bulbar function was included in base case, disutility for scoliosis and respiratory support included in scenario analyses but these have not been explored in EAG base case
- Recognise limited data available for disease complications but call for clear messaging that ICERs do not capture the full benefits associated with DMTs, so ICERs should be considered conservative

SMA UK+ (for other responses see sensitivity of motor function assessment tools key issue)

- EAG notes that 10% utility increment is a pragmatic placeholder rather than an empirical estimate
- SMA REACH-UK caregiver survey (n = 58) shows a mean EQ-5D-Y gain of 0.15 (QALY) (95 % CI 0.12 – 0.18) when a child moves from total feeding dependence to independent self-feeding
- Ask the Committee to either (a) apply the 1.7x severity modifier or (b) include a 0.15 within-state utility uplift so that fine-motor gains are more appropriately valued

Should an adjustment to utility values be made for uncaptured QoL gains? Should disease related complications be explicitly included in the model?

Consideration of inconsistent milestones used for health states included in supplementary appendix

DMT = disease-modifying therapy; ICER = incremental cost-effectiveness ratio;

Key Issue: Patient utilities for severe health states

EAG notes large variation in patient utility values, causing uncertainty

EAG

- There is large variation in utility values used for patients across previous appraisals (TA588, TA755, HST24)
- Size of modelled benefit is sensitive to utility values for severe health states
- Some values are close to, or worse than being in "dead" state, must reflect patient preferences appropriately
- EAG adopts increment approach (values from HST24 + 10% uplift for DMTs, same values for all types)

Table: utility values used for different health states in each company base case

Health state	Biogen base case for all SMA models	Roche base case for presymptomatic / type 1 SMA	Health state	Roche base case for type 2/3 SMA
Permanent ventilation	0	-0.02	Not sitting	-0.17
Not sitting	0.19	0.10	Sitting (supported)	0.04
Sitting	0.60	0.20	Sitting (unsupported)	0.04
Standing	0.77	0.70	Standing	0.56
Walking	General population	0.85	Walking	0.56
Additional utilities			Additional utilities	
DMT benefit	+0.1	N/A	Bulbar function	-0.17
Source	HST24	TA755	Source	Lloyd et al. 2019

Should utility values vary by SMA type? Which utilities should be used for each health state?

DMT = disease-modifying therapy;

Key Issue: Carer health-related quality of life

The companies adopt different approaches for including carer utility values

Background:

- **TA588/TA755:** committee said carer utility should be considered, but quantifying was extremely difficult
- **TA755:** company additive approach criticised by EAG because it assumed that after a patient died the caregiver health-related quality of life was zero. EAG used disutility approach, but committee uncertain as this approach resulted in 'carer QALY trap' for type 1 (↑ life-extension, ↓ cost-effectiveness)

Biogen

- Increment approach is preferred as this focuses on treatment-related improvements in caregiver well-being, aligning with the purpose of cost-effectiveness analysis which is to evaluate the impact of interventions
- This provides a clear link between patient health and carer benefits, also avoids carer QALY trap

Roche

- Given TA755 committee comments, use decrement approach; assume 2.2 or 3 carers (by health state/type)
- Biogen increment approach rewards occupancy of better health states via incremental gains and the Roche approach penalises occupancy of worse health states through decrements
- Utility outcomes differ due to different predicted survival and health state occupancy over time
- QALY trap can be avoided by bereavement disutilities and/or limiting carer disutility to BSC life expectancy
- Support EAG using Biogen approach for consistency, suggest asking experts if utility will vary by SMA type

QALY = quality adjusted life-year

For caregiver utility values see supplementary appendix

Key Issue: Carer health-related quality of life

The companies adopt different approaches for including carer utility values

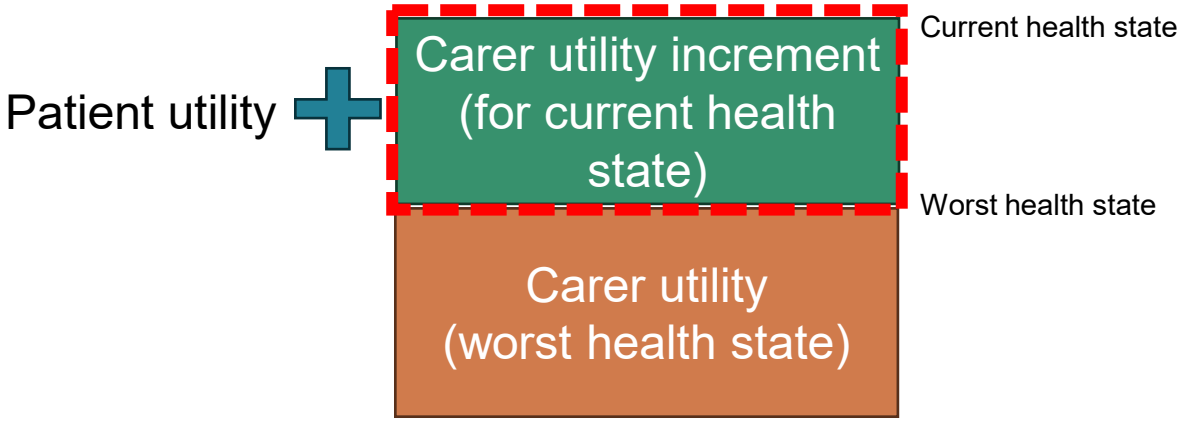
Biogen approach

- A utility **increment** for each health state is calculated using lowest health state as a baseline
- Same increments for all models, assuming it is health state, not SMA type that is important
- Assumes 1 carer (avoids using 2 carers for more severe states thus rewarding more severe states)
- Assumes carer increment = 0 after patient dies
- Rewards survival gains

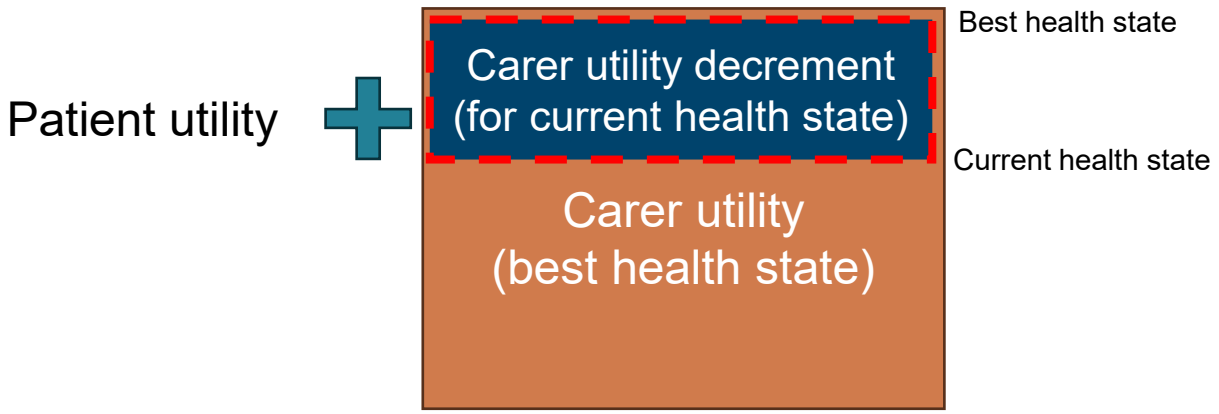
Roche approach

- A utility **decrement** for each health state is calculated using highest health state as a baseline
- After patient dies, decrement stops, carer QALYs ↑
- No adjustment for bereavement effect or 'carer QALY trap', as per expert opinion
- Does not reward survival gains
- Assume 2.2 carers per patient

Illustrative – not to scale



Positive impact on HRQoL for carers



Negative impact on HRQoL for carers

HRQoL = health related quality of life; QALY = quality adjusted life-year

Key Issue: Carer health-related quality of life

The companies adopt different approaches for including carer utility values

EAG

- Carer utility not included in EAG base case because of concerns with approach and robustness of data
- Unclear if carer utility varies by age, health state, SMA type, characteristics, duration, impact of stopping care
- Experts have highlighted significant impact on carer utility, so this is explored in limited scenario analyses
- Previously said Lo et al (2022) was preferred source of carer utility values, but have withdrawn that preference

Patient/Prof comments

Novartis: using data outside of clinical trials and lack of standardised approach for incorporating carer QoL are insufficient arguments for not including carer QoL in EAG base case, best approach is exploring scenarios for both treatments using the different approaches adopted by the two companies

SMA UK+: ICERs are sensitive to including carer QoL, excluding carer QoL is a missed opportunity and undervalues the immense workload and impact of SMA on families – qualitative data consistently shows the profound effect SMA has on carers' physical, emotional, and financial well-being

Should carer QALYs be included in the modelled base cases? If so, which approach should be used (increment, decrement, other)?
How many carers should be assumed? Should carer utility values vary by SMA type?
Which carer utility values should be used for types 2&3?

QALY = quality adjusted life-year; QoL = quality of life;

Key Issue: Carer health-related quality of life

Biogen uses the same carer utility values for all SMA types, Roche doesn't

- Biogen assumes that it is the health state, not the SMA type, that determines the impact on quality of life.
- Roche used different values for type 2/3

Health state	Biogen	Roche	
	All types	Presymptomatic / type 1 SMA	Type 2/3 SMA
Permanent ventilation	0.484	0.484	*(not applicable)*
Not sitting	0.484	0.484	0.700
Sitting (supported)	0.628	0.628	0.772
Sitting (unsupported)			0.843
Standing	0.771	0.771	0.915
Walking	Population norm	0.915	0.915
Number of carers	*1*	*2.2*	
Duration	*While patient is alive*	*While patient is alive*	
Source	Bastida et al. / Ara et al. (EAG preference from TA755)		

Note: increase in carer utility value by health state does not correspond closely with increase in patient utility

BSC = best supportive care
DMT = disease modifying therapy
MAA = managed access agreement
QALY = quality adjusted life-year

Key Issue: Treatment discontinuation

Companies use different approaches to model treatment discontinuation

EAG

- Roche models did not include discontinuations for risdiplam or nusinersen (other than stopping if perm vent)
- Biogen included discontinuation, likely overestimates discontinuation as based on short-term MAA follow-up
- Biogen discontinuations assume people go onto BSC, but people may switch to alternative DMTs
- EAG removed stopping rule for perm. vent. patients in Roche model, but kept stopping rule in Biogen model
- Perm. vent. patients taking treatment is appropriate in Roche model as they receive QALY benefit; impact on ICER is negligible; easier to administer risdiplam to perm vent patients vs nusinersen.

Roche

- Roche models do include treatment discontinuation – uses health-state-specific stopping rule, whereby patients in lower health states no longer incur treatment costs once the treatment effect is lost
- The EAG models do not include these rules and appear to assume lifelong treatment
- Models should be consistent and aligned with MAAs for nusinersen / risdiplam (stop treatment if perm vent.)

Biogen

- Query Roche approach: assuming no discontinuation is inappropriate as MAA data shows it happens
- No discontinuation likely overestimates benefit as on treatment utility increment is maintained for lifetime

Novartis: agree with EAG concerns, also think people discontinuing nusinersen would not have BSC

NICE

How should treatment discontinuation be modelled? Should the models assume that permanently ventilated patients continue treatment with risdiplam, but not nusinersen?

Key Issue: Costs for severe health states

EAG notes uncertainty in health state costs due to large variation in estimates

EAG

- Large variation in costs between companies for more severe health states which significantly impacts ICERs
- EAG base case adopts the same approach as Biogen (with costs inflated to most recent year)

Biogen:

- Health state costs in HST24 were accepted by EAG, so these costs have been used in Biogen models
- **HST 24: "**The company sourced health state [unit] costs from NHS Reference Costs 2019-2020, the NHS Business Services Authority prescription cost analysis 2021/22 and the literature. Where appropriate, costs were inflated to 2021 prices"

Roche:

- SLR revealed limited robust evidence on indirect costs associated with SMA
- A database feasibility study using CPRD and HES faced challenges in identifying SMA health states due to lack of motor milestone data, leading to the use of proxy variables and expert consultation
- Roche conducted a modified Delphi panel to gather expert consensus, revealing high health state costs and frequent interventions, costs were validated by clinical experts and patient advocacy groups
- Not clear why costs from Roche HCRU study not used by EAG. Unclear how the costs sourced from HST24 were originally calculated – precedent alone should not serve as rationale for use

CPRD = clinical practice research datalink; HCRU = healthcare resource utilisation; HES = hospital episodes statistics; ICER = incremental cost-effectiveness ratio

Key Issue: Costs for severe health states

EAG notes uncertainty in health state costs due to large variation in estimates

Table: annual costs used for different health states in each company base case

Health state	Biogen	Roche: presymp / type 1 SMA
Permanent ventilation	£283,710	Child: £18,684 / Adult: £9,132 One-off costs: £15,834
Not sitting	£112,500	Child: £23,592 / Adult: £8,364 One-off costs: £15,547
Sitting	£67,567	Child: £18,048 / Adult: £6,252 One-off costs: £12,964
Standing	£8,333	Child: £11,868 / Adult: £2,268 One-off costs: £7,359
Walking	£8,333	Child: £4,968 / Adult: £1,452 One-off costs: £3,702
Source	HST24	Roche HCRU study

Health state	Roche: type 2/3 SMA
Not sitting	Child: £18,972 / Adult: £8,364 One-off costs: £15,586
Sitting (supported)	Child: £15,780 / Adult: £6,252 One-off costs: £9,456
Sitting (unsupported)	Child: £15,780 / Adult: £6,252 One-off costs: £9,456
Standing	Child: £7,920 / Adult: £2,268 One-off costs: £2,372
Walking	Child: £2,664 / Adult: £1,452 One-off costs: £715
Source	Roche HCRU study

What health state costs should be used?
Should health state costs vary by SMA type and by adults and children?

HCRU = healthcare resource utilisation

Key issue: High background care costs

High background care costs for type 1 SMA may penalise extended survival

NICE methods manual 4.4.16

"In cases where a technology increases survival in people for whom the NHS is currently providing care that is expensive or would not be considered cost-effective at NICE's normal levels, the committee may consider alongside the reference-case analysis a non-reference-case analysis with the background care costs removed"

Previous appraisals

- Removing high background care costs has been explored in previous appraisals, but not used as formal committee preference. Background care costs not excluded in TA588 or TA755
- High social care costs were removed in a scenario in HST24, but not used by committee as results unchanged

Biogen

- Provide scenario with Type 1 SMA health state costs removed for period of extended survival with nusinersen due to very high background care costs

EAG

- Shared scenarios with 1) background costs removed entirely for all treatments and 2) removed for the intervention for the period of extended survival versus the comparator

Should background care costs be removed for cost-effectiveness results?

Key Issue: Severity modifier

The companies and EAG estimate different severity modifier weights compared to BSC

Background

- NICE manual: *"the committee will consider the severity of the condition, defined as the future health lost by people living with the condition with standard care in the NHS"*
- *This means carer QALYs should not be included in the severity modifier calculations*

Table: QALY weights in NICE health technology evaluations manual

QALY weight	Prop. shortfall	Abs. shortfall
1	<0.85	<12
x1.2	0.85 to 0.95	12 to 18
x1.7	>=0.95	>=18

EAG base case	Expected QALYs	BSC QALYs	Absolute shortfall	Proportional Shortfall	EAG severity modifier	Company severity modifier***
Biogen - nusinersen						**Biogen**
Presymptomatic	24.89	[redacted]	[redacted]	[redacted]	1.2	1.2/1.7*
Type 1	24.87	[redacted]	[redacted]	[redacted]	1.7	1.7
Type 2&3	24.55	[redacted]	[redacted]	[redacted]	1.2	1.2
Roche - risdiplam						**Roche**
Presymptomatic	24.87	[redacted]	[redacted]	[redacted]	1.7	1.7
Type 1	24.87	[redacted]	[redacted]	[redacted]	1.7	1.7
Type 2&3	24.02	[redacted]	[redacted]	[redacted]	1.2	1.7**

*both modifiers considered to ensure consistency between company models **Roche says 1.7 should be used as threshold is met in Roche base case, and nearly met in EAG base case, without accounting for uncaptured utility changes ***do not include carer QALYs
Abbreviations: Abs. = absolute; BSC = best supportive care; prop. = proportional; QALY = quality adjusted life year

Key Issue: Severity modifier

The companies and EAG estimate different severity modifier weights compared to BSC

Background

- Severity modifier not part of NICE methods during past appraisals, end of life criteria used instead
- **TA588/TA755:** end of life criteria met for Type 1 SMA but not Type 2 or 3 SMA (due to survival > 2 years)

EAG

- As the severity modifier criteria is based on long term prognosis, differences in modelled prognosis in the respective models (due to clinical and population differences in the data and health state definitions) led to different predicted prognosis and differences in the severity modifier weight used

Roche and Biogen

- Understand that nusinersen and risdiplam populations are clinically different
- But inappropriate for the same populations in the models to have a different severity modifier applied

Stakeholders

Novartis: BSC is not a suitable comparator so it should not be used for severity calculations
Patient groups: combining patient and carer QoL jeopardises severity calculations and should be separated

What QALY weighting for severity should be applied for each population and model?

BSC = best supportive care; QoL = quality of life

Cost-effectiveness results

Cost-effectiveness results are confidential and will be presented in Part 2 of this meeting

SMA type	Nusinersen vs BSC (Biogen model)	Nusinsersen vs BSC (EAG model)	Risdiplam vs BSC (Roche model)	Risdiplam vs BSC (EAG model)
Presymptomatic SMA	ICERs within normal cost-effectiveness range			
Type 1 SMA	ICERs above normal cost-effectiveness range			
Type 2/3 SMA	ICERs above normal cost-effectiveness range			

BSC = best supportive care; ICER = incremental cost-effectiveness ratio

Key questions for committee

Are the starting/stopping rules from MAA appropriate for routine commissioning?
Why do some SMA groups not currently have access to treatments? Are there any equality implications to consider in relation to these groups? Are there any other equality issues not captured here?
Are the ITCs suitable for decision making?
Which comparators are appropriate for each population? Given data limitations, which comparators can be considered for each population? Should BSC followed by symptomatic treatment be a comparator for presymptomatic population?
Are relevant functional changes captured in the economic evaluation?
How can the lack of data for Types 0 and 4 SMA be considered in decision making?
What assumptions and inputs for the Biogen and Roche models would be expected to be the same?
Should an adjustment to utility values be made for uncaptured QoL gains? Should disease related complications be explicitly included in the model?
What patient utilities should be used for each health state and SMA type?

BSC = best supportive care; ITC = indirect treatment comparison; MAA = managed access agreement; QoL = quality of life

Key questions for committee

Should carer QALYs be included in the modelled base cases? If so, which approach should be used (increment, decrement, other)? How many carers should be assumed? Which utility values should be used for types 2&3?
How should treatment discontinuation be modelled? Should the models assume that permanently ventilated patients continue treatment with risdiplam, but not nusinersen?
What health state costs should be used? Should health state costs vary by SMA type and by adults and children?
Should background care costs be removed for cost-effectiveness results?
What QALY weighting for severity should be applied for each population and model?
What is the committee's preferred ICER threshold for each SMA type?
What is the committee's preferred ICER for each SMA type? Is additional analysis needed to define this?

QALYs = quality adjusted life years; ICER = incremental cost-effectiveness ratio

Supplementary appendix

NICE National Institute for Health and Care Excellence

Patient perspectives – SMA disease burden

I watched my son deteriorate and lose many abilities such as: crawling, high kneeling, rolling, arm strength and neck strength. I also had to watch his respiratory system decline, resulting in multiple hospital admissions.

If I lost the ability to use a mouse there's a good chance I'd also lose my ability to do my job. As the sole bread winner within my family this would have a catastrophic impact. These are the details that people don't understand.

My son's bedroom looks like a hospital with a ventilator for sleeping, a suction machine, cough assists and a saturation monitor.

Those with SMA face this continuous grieving process over and over again throughout their entire life due to the progressive ongoing loss of different functions over time. Often described as a "chronic sorrow"

[name] has been entirely tube-fed since he was 6 months old and requires regular suctioning to manage his secretions. He thoroughly enjoys tasting food and is very happy to munch on anything and then spit it out, but tasting has to be very carefully monitored due to the high risk of choking.

[name] (7yrs) has a huge vocabulary, above average for his age and is able to hold meaningful, interesting and often witty conversations. But his articulation and volume of speech are significantly affected by SMA. If you don't know him well, he can require interpretation.

I have a constant "sword of Damocles" hanging over my head as to what function I am going to lose next, all of which has an indescribable impact on my mental health.

Impact on carers and family

I had to accept the need to give up my career as a primary school teacher to care for [name] full time. This put enormous strain on our finances and caused a significant amount of stress.

Even local trips require meticulous planning, organising and packing, taking a myriad of machines, wheelchairs, medical feed and extra medical stock to ensure any eventuality is catered for. Daytrips are similarly stressful and frustrating for my 10-year-old daughter (sibling), with so many activities out of bounds for us as a family.

My son's physical needs consisted of dressing, toileting, bathing, washing, assisting with meals and snacks throughout the day, getting [name] anything he needed, changing his position throughout the day from the floor, to wheelchairs or turning him throughout the night. Ultimately, being there to assist him 24/7

My health issues always come second, as my children will always come first

I had the pressures of multiple, weekly appointments, the fight to get my son the support he needed and the financial implications this all had, especially when trying to source vital equipment that the NHS wouldn't supply.

Even when I have the opportunity to sleep, I can't, for fear of not hearing my son or not acting quickly enough

[name] also has a sister, 11 months older...I had immense feelings of guilt as I had to prioritise [name]

Transferring [name] is becoming more and more difficult and is having a detrimental effect on my back.

Benefits of treatment for patients and carers

I no longer have that sword of Damocles hanging over me, no longer am I waking up in the morning wondering if I've lost a function, no longer only grieving what I've lost, I am able completely focused on what I have and look forward to the rest of my life.

The perception of lower efficacy in older population is far from the truth. Yes improvements are a bonus, but stability maintains lives, livelihoods, relationships and everything else.

I can eat and drink without worrying about of choking and no longer have to consider the thought of dying each time I sit down for a meal.

I was told I probably wouldn't live beyond 40. Now all of a sudden my outlook on life has changed. Treatment has given me hope that while I may not live to 100, there is now no predefined expiry date that I am living to.

My son's school attendance has risen from 27% to 98% and he is now one of the top students in his class.

The value of not losing a critical ability such as the movement in a finger to control a powerchair or the ability to swallow food, cannot be emphasised enough.

Risdiplam has transformed [name] life for the better and continues to gain strength and new abilities along with this treatment and regular physio.

Benefits of treatment for patients and carers

My son's improved strength has allowed me to be needed less, so I have more quality time with my daughter

Since my son has been on risdiplam, he has not had a hospital admission, his lung capacity has increased, he has regained his swallow and the threat to his life is no longer as severe. This has had a massive impact on not only his quality of life but his family's too

Living with SMA brings huge amounts of stress, anxiety and financial burden. With treatment it can also bring huge amounts of pride, joy and a new appreciation of every moment.

Nusinersen treatment and effective management strategies have enabled [name] to not only live but to live a happy and full life. He is thriving.

EAG qualitative analysis - Quotes

"Before the MAA there were no defined pathways for adults with SMA. There was significant local variation in care (e.g. frequency of follow-up in neurology clinic, respiratory monitoring and access with physio) depending on the local interests of the neurologist and availability of neuromuscular specialist neurologists" *Association of British Neurologists*

"Orthotics provision is fragmented nationally as well as management of orthopaedic problems." *Professional expert.*

"Unfortunately, physio comes in blocks on the NHS so it is not continuous throughout the year. These voids are filled with paid, private physio." *Carer for child with SMA: Patient expert submission.*

"I have also been suffering with a stage 2 sore on my coccyx which limits the amount of time I can stay up in my electric wheelchair to half a day which is difficult to accept and adapt my life round this problem due to lack of care hours that are available to me." *Adult (input to registry) 58y, 2.4y on risdiplam.*

"He is dependent on his parents as its a struggle to get carers" *Adult (input to registry) 27y, 2.3y on risdiplam.*

"Fundraising has been necessary to ensure our child gets the correct care to provide things like orthotics and private physiotherapy and other equipment that the NHS have been unable to provide" *Carer of child with SMA: SMA UK/MD UK/Treat SMA submission.*

"[…] the financial implications this all had, especially when trying to source vital equipment that the NHS would not supply. I had to fundraise as this was my only option to purchase this equipment, which was another thing I had to take ownership of." *Carer for child with SMA: Patient expert submission.*

Treatment eligibility criteria – Managed Access

Nusinersen eligibility criteria (MAA)	Risdiplam eligibility criteria (MAA)
• No permanent ventilation (≥16 hours/day for 21 consecutive days in the absence of acute reversible infection) or tracheostomy requirement at baseline	
• Nusinersen or risdiplam is used as a monotherapy	
• Must not have had successful treatment with onasemnogene abeparvovec	
• Intrathecal injection must be technically feasible in the opinion of the treating clinician and not contraindicated	
• Must not have received spinal fusion surgery following a diagnosis of scoliosis which, in the opinion of the treating clinician, prohibits safe administration	
• Must not have severe contractures that, in the opinion of the treating clinician, prohibit measurement of motor milestones	

Stopping criteria: nusinersen and risdiplam

If a patient meets any of the stopping criteria the treating clinician should decide whether to terminate or continue treatment:

- the patient is diagnosed with an additional progressive life-limiting condition where treatment would not provide long- term benefit such as terminal cancer or catastrophic brain injury.
- the patient uses a different disease-modifying therapy to treat SMA.
- the patient is not receiving benefit from treatment, as confirmed either by the annual additional Blueteq form or by meeting any of the stopping criteria within Table

Endpoint	Proposed Assessment	Stopping Rule
Motor Function	Current Gross WHO motor milestone, using appropriate scale based on patient motor ability: - HINE - Revised Hammersmith Scale (RHS) - CHOP INTEND - RULM A scale is chosen at therapy initiation and ideally used throughout. If a change is needed due to clinical status, a final reading of the old scale is taken alongside the baseline of the new scale.	Total worsening in scale score corroborated by two consecutive measurements*: - >2 points on horizontal kick or 1 point on other HINE scores (excluding voluntary grasp) - >4 points on CHOP INTEND - >3 points on RHS *To confirm true decline, not an “off” day. **If a domain becomes unmeasurable (e.g. due to contractures), scores are scaled proportionally.
Ventilation Requirement	Track incidence, duration, and type of ventilation. Monitor pneumonia rates.	Permanent ventilation (≥16 hours/day for 21 consecutive days without acute reversible infection) or permanent tracheostomy insertion.
Scoliosis (for nusinersen only)	Assess scoliosis progression and impact on intrathecal administration.	Inability to administer nusinersen intrathecally due to spinal fusion surgery.
Survival	Assess mortality from any cause and SMA-related mortality using ICD-10 coding on death certificates (Part I and II).	All patients stop due to mortality.

Starting/Stopping criteria: NHSE perspective

- Current MAAs include stopping rules, considering motor function, ambulation and ventilation requirement
- Assessment of benefit is best considered through tailored case-by-case assessments, within an overarching framework, considering:
  - Challenges in defining respiratory deterioration – motor response may be sufficient
  - For adult populations, treatment benefits most commonly be reflected in stability
  - Particularly difficult to assess benefit in severely disabled patients; fine motor skills (which aren't currently measured) can be important and of valuable benefit
  - Meaningful treatment responses are not all measured in systematic way e.g. stamina
  - Challenges in monitoring benefit in a patient who is growing (children and young adults) – increase in weight can lead to loss of power, but doesn't constitute treatment failure
- Objective commissioning framework should be balanced with opportunity for expert opinion (accounting for complexity/nuance)
- Most frequent request to Clinical Panel is to use risdiplam/nusinersen following poor response to gene therapy. Also received requests for pre-natal use, which is off-label.

Measurement scales used in SMA type 1

Measure	Description	Clinically meaningful improvement
SMA Type 1		
CHOP INTEND	• 16-items, scored 0 – 4 each. • Assesses active and reflexive movements, such as upper and lower extremities, hand grasping, rolling, head control	Score change ≥ 4
HINE-2	• 8 motor milestones • Head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing and walking	Achievement of milestones and higher scores (> 2-point increase in ability to kick and >1-point increase in head control, rolling, sitting, crawling, standing / walking)
BSID-III	BSID measures cognition, language, motor skills (fine and gross motor skills), socio-emotional behaviour, adaptive behaviour	Ability to achieve a sitting position unsupported at 12 months
WHO motor milestones	Tracks gross motor development milestones in infants and young children	Achievement of milestones not expected under natural course of SMA
6MWT	Distance walked in 6 minutes	≥30 meters increase in walking distance from baseline

Measurement scales used in SMA types 2 & 3

Measure	Description	Clinical meaningful improvement
SMA Type 2 and Type 3		
MFM32	• 32 items in 3 domains (standing and transfers; axial and proximal motor function; distal motor function). • Scored 0 – 3, summed and transformed onto 0 – 100 scale, expressed as %.	• Change of ≥0 in MFM32 total score representing stabilisation or improvement • > 3 points should be marked as improvements for patients
RULM	• Upper limb motor function (elbow, wrist and hand); 19 items, scored on a scale between 0 – 2 except 1 that is scored between 0 – 1). • Total score of 0 – 37 is estimated.	Change of > 2 on RULM represents an estimate of a meaningful improvement in motor function.
HFMSE	• Measures sitting, rolling, crawling, kneeling and standing/stepping • 33 items inc. standing transfers, ambulation and proximal and axial function, scored 0 – 2 (max 66 points)	Change of > 3 points in HFMSE demonstrates meaningful improvement in motor function

Pivotal clinical trials – Presymptomatic SMA

Intervention	Nusinersen	Risdiplam
Name	**NURTURE**	**RAINBOWFISH**
Design	Phase II, open-label, multicentre, single-arm study	Phase II, open-label, multicentre, single-arm study
Intervention	Nusinersen (n = 25)	Risdiplam (n = 26)
Comparator	None	None
1° outcome	Event-free survival	Sitting without support at 12 months
Key 2° outcomes	• Overall survival • Motor milestones (WHO and HINE-2) • CHOP INTEND, HFMSE, growth • Onset of clinical SMA	• Survival and permanent ventilation • Motor milestones (WHO, BSID-III) • CHOP INTEND, HFMSE, growth • Onset of clinical SMA
Follow-up	Median of 4.9 years (3.9-5.7)	12 month outcomes
Additional data available for MTA	+ ~7 years of follow up Previous follow-up was ~10.5 months	+ ~12 months of follow-up Previous follow-up was 12 months

Pivotal clinical trials – Type 1

Intervention	Nusinersen	Risdiplam
Name	**ENDEAR + SHINE extension**	**FIREFISH**
Design	Phase III, randomised, double-blind, multicentre, sham-controlled study	Open-label, multicentre study with two parts: dose finding and confirmatory
Intervention	Nusinersen (n = 80)	Risdiplam (n = 41)
Comparator	Sham-control (n = 41)	None
1° outcome	• Motor milestone responders (HINE-2) • Event-free survival	Sitting without support at 12 months
Key 2° outcomes	• CHOP INTEND responders • CMAP responders • Mortality or permanent ventilation	• Survival and permanent ventilation • Motor milestones (BSID-III) • CHOP INTEND, HINE-2
Follow-up	[redacted]yrs	Up to 60-month outcomes
Additional data available for MTA	[redacted]yrs	+36 months additional follow up Previously 24-month outcomes

Pivotal clinical trials – Types 2 & 3

Intervention	Nusinersen	Risdiplam
Name	**CHERISH + SHINE extension**	**SUNFISH**
Design	Phase III, randomised, double-blind, multicentre, sham-controlled study	Multicentre, randomized, double-blind, placebo-controlled study with two parts: dose finding and confirmatory
Intervention	Nusinersen (n = 84)	Risdiplam (n = 120)
Comparator	Sham-control (n = 42)	Placebo (n = 60)
1° outcome	Change in HFMSE score at 15 months	Change in MFM-32 score at 12 months
Key 2° outcomes	• Large HMFSE score increases • Motor milestones • Change in RULM score at 15 months	• Large MFM-32 score increases • Motor milestones • Change in RULM score at 12 months
Follow-up	[redacted]	<5 years
Additional data available for MTA	+~4yrs additional follow-up	+36 months additional follow up Previously 24-month outcomes

Adult MAA: Registry data collected

Data on ~[redacted] adults with SMA collected from 17 centres across England

	Nusinersen	Risdiplam
Number of adults	[redacted]	[redacted]
Cohorts	[redacted]	[redacted]
Follow-up	[redacted]	[redacted]
Outcomes	• Motor function (e.g. WHO Motor Milestones, RULM, ATEND) • Survival and ventilation • Respiratory function • Treatment discontinuation • PROMs (inc. EQ-5D, SMA independence scale and free-text)	

Paediatric MAA: Registry data collected

Data on ~[redacted] children with SMA collected from 17 centres across England

	Nusinersen	Risdiplam
Number of children	[redacted]	[redacted]
Cohorts	[redacted]	[redacted]
Follow-up	[redacted]	[redacted]
Outcomes	• Motor function (e.g. WHO Motor Milestones, HINE-2, CHOP-INTEND, RHS, RULM) • Survival and ventilation • Treatment discontinuation • PROMs	

Company and EAG base cases – presymptomatic

Input	Nusinersen (Biogen)	Nusinersen (EAG)	Risdiplam (Roche)	Risdiplam (EAG)
Time horizon	100 years	-	[redacted]	100 years
Intervention effectiveness	NURTURE	-	RAINBOWFISH	-
Relative effectiveness	vs. BSC: ENDEAR and CHERISH trials	- Plus scenario vs OA uses MAIC	Equal efficacy vs OA and nusinersen vs. BSC: internal natural history study	- Plus naïve comparison vs nusinersen
Treatment effect duration*	Nusinersen: 72 months (decline after this from ENDEAR / CHERISH) BSC: 15 months (decline after this from Wadman et al.)	- Plus for scenario vs OA, treatment effect duration and decline after assumed equal to nusinersen	After 10 years receiving DMTs only maintained the motor milestones achieved	Risdiplam: 72 months (decline after this from type 1/2/3 models) BSC: 15 months (decline after this from Wadman et al.)

*After treatment effect, people either maintain or lose motor milestones (but they cannot gain higher motor milestones); Roche raises concerns with EAG approach due to declining treatment effectiveness and incorrect modelling of decline

- indicates no change or minor change from company base case (e.g. update for inflation/latest data)

Company and EAG base cases – presymptomatic

Input	Nusinersen (Biogen)	Nusinersen (EAG)	Risdiplam (Roche)	Risdiplam (EAG)
Survival	OS from HST24 for worst 3 health states UK general mortality for best 2 health states Nusinersen and BSC assumed equal survival	- Nusinersen vs OA, survival assumed equal	General UK population	OS for sitting without support, not sitting, and permanent ventilation from HST24
Treatment discontinuation	Based on MAA data	- plus no discontinuation for OA in scenario	Perm. vent. patients stop treatment. No other discontinuation.	Perm vent patients are treated. (see key issue)
Health state utility values	From HST24 + 10% uplift for DMTs	- plus scenario vs OA, OA also had 10% uplift	Based on TA755	From HST24 + 10% uplift for DMTs; values adjusted for age / sex
Adverse events	Not included	-	Add 2 disease related events for BSC (not treatment related)	Removes events for BSC, assume already captured in state
Carer utility	EAG pref. from TA755	Not in base case, scenario using Lo et al	EAG pref. from TA755	Not in base case, scenario using Lo et al
Health state costs	HST24 and TA755	- *(plus inflation)*	Expert opinion	HST24 and TA755

Company and EAG base cases – Type 1

Input	Nusinersen (Biogen)	Nusinersen (EAG)	Risdiplam (Roche)	Risdiplam (EAG)
Time horizon	100 years	-	[redacted]	100 years
Intervention effectiveness	Nusinersen: ENDEAR and SHINE	-	Risdiplam: FIREFISH	-
Relative effectiveness	BSC: ENDEAR trial	- Plus scenario vs OA uses MAIC of STR1VE data	Nusinersen and BSC: unachored MAIC using ENDEAR data OA: STRIVE-EU	Nusinersen and BSC: Ribero et al (FIREFISH/ENDEAR) OA: STRIVE-EU
Treatment effect duration*	Nusinersen: 60 months (decline after this from ENDEAR) BSC: 12 months (decline after this from Wadman et al.)	- Plus for scenario vs OA, treatment effect duration and decline after assumed equal to nusinersen	After 2 years: DMTs cannot worsen milestones, BSC cannot improve After 5.5 years: all treatments maintain milestones achieved	Risdiplam: 60 months (decline after this from HINE-2 response from Ribero et al.) BSC: 12 months (decline after this from Wadman et al.)

*After treatment effect, people either maintain or lose motor milestones (but they cannot gain higher motor milestones); Roche raises concerns with EAG approach due to declining treatment effectiveness and incorrect modelling of decline

[-] indicates no change or minor change from company base case (e.g. update for inflation/latest data)

Company and EAG base cases – Type 1

Input	Nusinersen (Biogen)	Nusinersen (EAG)	Risdiplam (Roche)	Risdiplam (EAG)
Survival	OS from ENDEAR/ SHINE for worst 3 health states UK general mortality for best 2 health states	- Plus for nusinersen vs OA scenario, survival assumed equal	OS from FIREFISH informed survival for "not sitting" and "sitting" states only	FIREFISH survival adjusted by UK mortality in long term Mortality at permanent ventilation with DMTs = mortality with BSC
Treatment discontinuation	Based on MAA data	- Plus no discontinuation for OA in scenario	Perm. vent. patients stop treatment. No other discontinuation.	Perm vent patients are treated. (see key issue)
Health state utility values	From HST24 + 10% uplift for DMTs	- Plus for scenario vs OA, OA also had 10% uplift	Based on TA755	From HST24 + 10% uplift for DMTs; values adjusted for age / sex
Adverse events	Not included	-	Add 2 disease related events for BSC (not treatment related)	Removes events for BSC, assume already captured in state
Carer utility	EAG pref. from TA755	Not in base case, scenario using Lo et al	EAG pref. from TA755	Not in base case, scenario using Lo et al
Health state costs	HST24 and TA755	-	Expert opinion	HST24 and TA755

Company and EAG base cases – Type 2/3

Input	Nusinersen (Biogen)	Nusinersen (EAG)	Risdiplam (Roche)	Risdiplam (EAG)
Time horizon	100 years	-	[redacted]	90 years
Intervention effectiveness	Nusinersen and BSC: CHERISH and SHINE	-	Risdiplam: SUNFISH	-
Relative effectiveness	BSC: CHERISH and SHINE trials	-	Nusinersen: CHERISH BSC: SUNFISH control arm	- Plus scenario with Ribero et al
Treatment effect duration*	Nusinersen: 96 months (decline after this from CHERISH) BSC: 15 months (decline after this from Wadman et al.)	-	After 60 months receiving DMTs only maintained or improved the motor milestones achieved	Risdiplam: 96 months (decline after this from SUNFISH) BSC: 15 months (decline after this from Wadman et al.)

*After treatment effect, people either maintain or lose motor milestones (but they cannot gain higher motor milestones); Roche raises concerns with EAG approach due to declining treatment effectiveness and incorrect modelling of decline

- indicates no change or minor change from company base case (e.g. update for inflation/latest data)

Company and EAG base cases – Type 2/3

Input	Nusinersen (Biogen)	Nusinersen (EAG)	Risdiplam (Roche)	Risdiplam (EAG)
Survival	OS from HST24 for worst 3 health states UK general mortality for best 2 health states Nusinersen and BSC assumed equal survival	-	Type 2: SLR survival curves pooled Type 3: survival same as general population HR of 0.75 for risdiplam / nusinersen vs BSC for OS	HST24 for "not sitting" and "sitting“ UK mortality for "standing" / "walking" Survival gains due to disease improvements
Treatment discontinuation	Based on MAA data	-	Perm. vent. patients stop treatment. No other discontinuation.	Perm vent patients are treated (see key issue)
Health state utility values	From HST24 + 10% uplift for DMTs	- Scenarios using Roche utility values	Vignette study from Lloyd et al. 2019	From HST24 + 10% uplift for DMTs; values adjusted for age / sex
Adverse events	Not included	-	Add 2 disease related events for BSC (not treatment related)	Removes events for BSC, assume already captured in state
Carer utility	EAG pref from TA755.	Not in base case, scenario using Lo et al	EAG pref from TA755.	Not in base case, scenario using Lo et al
Health state costs	HST24 and TA755	-	Expert opinion	HST24 and TA755

Inconsistent motor milestones in health states

Different trials and models use different measures for motor milestones

EAG

- The motor milestone scores used in defining disease progression in model health states are derived from different tools which vary in their scoring system
- Assuming equivalence between health states defined by different tools may introduce uncertainty around motor functions, patient health states and cost-effectiveness results

Roche

- Motor function assessments conducted are chosen depending on age and functional ability with reported advantages and disadvantages of each scoring system, including overlap in assessments that may be used
- Each scale rates individuals differently, not possible to directly translate scores from one scale to another
- Suggest that clinical expert advice is sought to assess the appropriateness of comparing scales

Biogen

- Query how distinct health state definitions are in Roche model when each state could include people with a broad range of abilities, also unclear how well costs and utilities reflect the diversity within states

Is it appropriate to assume equivalence between health states in the different models?

Inconsistent motor milestones in health states

Different trials and models use different measures for motor milestones

Biogen presymptomatic and type 1 model			Roche presymptomatic and type 1 model	
Model states	**WHO motor milestones**	**HINE-2 definitions**	**Model states**	**HINE-2 definitions**
Not sitting	-	< 3 in HINE-2 sitting	**Not sitting**	< 1 in HINE-2 sitting
Sitting without support	Sitting without support	≥ 3 in HINE-2 sitting to < 2 in standing	**Sitting (with or without support)**	≥ 1 in HINE-2 sitting to < 2 in standing
Standing with support	Standing with assistance	≥ 2 in HINE-2 standing to < 3 in walking	**Standing (with or without support)**	≥ 2 in HINE-2 standing to < 2 in walking
Walking independently	Walking alone	≥ 3 in HINE-2 walking	**Walking (with or without support)**	≥ 2 in HINE-2 walking

Inconsistent motor milestones in health states

Different trials and models use different measures for motor milestones

Biogen Type 2/3 model		Roche Type 2/3 model	
Model states	WHO motor milestones	**Model states**	MFM-32/HFMSE item and score
Not sitting	-	**Not sitting**	Item 9 (maintain seated position) = 0 (not able to maintain)
Sitting without support	Sitting without support	**Sitting with support**	Item 9 (maintain seated position) = 1 (able to perform but not finish)
		Sitting without support	From Item 9 (maintain seated position) = 2 (able to perform with some help) to Item 25 (maintain standing position) < 1 (able to perform but not finish)
Standing with support	Standing with assistance to standing alone	**Standing (with or without support)**	From Item 25 (maintain standing position) = 1 (able to perform but not finish) but HFMSE score not in highest current level of independent mobility
Walking independently	Walking alone	**Walking (with or without support)**	HFMSE 'level of independent mobility: highest current level of independent mobility'

Key Issue: Carer health-related quality of life

EAG uses values sourced from Lo et al. in its carer QALY scenarios

Table: carer utility increments and decrements used in EAG scenarios

Model state	Decrements approach	Increments approach
Permanent ventilation	-0.408	Baseline
Not sitting	-0.408	0.000
Sitting (supported)	-0.222	0.186
Sitting (unsupported)	-0.222	0.186
Standing	-0.068	0.340
Walking	Baseline	0.408
Source: produced by the EAG based on health utilities from Lo et al. 2022		

Lo et al: 'The utility loss associated with experiencing loss of motor function at the worst level ('cannot sit') is thus estimated as 13.8/33.9 = − 0.408 compared with the reference category ('can sit, stand and walk independently for more than 10 m'.

QALY = quality adjusted life-year