

Spinal muscular atrophy: nusinersen (MAA review of TA588) and risdiplam (MAA review of TA755) [ID6195]

Produced by Newcastle University

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1 Abstract

Background

Spinal muscular atrophy (SMA) is a rare genetic condition that causes muscle weakness and loss of function over time. In the most severe form untreated SMA results in death in infancy or early childhood.

Aim

The Newcastle Evidence Assessment Group (EAG) were asked by the National Institute of Health and Care Excellence (NICE) to assess the clinical and cost-effectiveness of two treatments for SMA: nusinersen and risdiplam.

Methods

The EAG consulted with the companies (Biogen, Roche), professional organisations, clinicians and patient organisations throughout. A qualitative framework analysis was undertaken using information provided to NICE, discussions between the EAG and patient and professional organisations, and free-text data provided by SMA registries.

The EAG updated the original systematic literature reviews (SLR) of clinical and economic evidence to March 2025. Conference abstracts, excluded from the original review, were included. Controlled studies and economic evaluations were critically appraised using standard tools. Data were narratively synthesised according to the drug, SMA type and outcome measure assessed. Reports from the Managed Access Agreements (MAA) for nusinersen and risdiplam from adult and paediatric registries, were critically assessed.

The EAG reviewed and critiqued company submissions including clinical and economic evidence and the economic models and the evidence used to parameterise these for each population group, including additional information submitted following points for clarification.

The EAG conducted its own economic analyses, drawing on evidence and models submitted by both companies. Because of the differences in population characteristics for nusinersen and risdiplam treatments, the treatments were evaluated using separate models. However, efforts were made to align the analyses for consistency and to address the key uncertainties surrounding the cost-effectiveness of each therapy within the context of the decision problem.

Results

The qualitative analysis suggested that treatment may maintain or improve motor, bulbar and respiratory function in those with SMA. However, it was not always possible to determine which treatment people had received. The insensitivity of tools to identify improvements in fine motor skills between motor milestones and the importance of these smaller improvements in motor function, and the importance of maintenance of function were also emphasised.

The updated SLR included 147 studies. For nusinersen 130 studies (22 new) were included, (three RCTs, eight controlled studies, 119 single arm studies). Thirteen studies (three new) assessed risdiplam, (one RCT, 12 single arm studies). Four studies (three new) included patients on both treatments, (one non-randomised controlled study, three single arm studies). Twenty were ongoing. The SLR results suggested both nusinersen and risdiplam, separately, improved or maintained motor function for people with presymptomatic and types 1 to 3 SMA. There is less evidence, and no controlled studies, that include presymptomatic patients. For nusinersen, some studies reported differences in effectiveness between population subgroups

in relation to age and SMA type. Evidence also suggested that nusinersen provided stability for respiratory function, while the evidence on risdiplam suggested mixed effects on ventilation. Separately, both showed mixed results regarding impact on bulbar function and quality of life measures in carers and patients. Importantly, there were higher survival rates amongst type 1 patients treated with nusinersen, and for both treatments survival was substantially higher than is the case for untreated type 1 patients. However, for risdiplam, there was a lack of controlled studies providing evidence on mortality. Adverse events were generally not serious for either nusinersen or risdiplam. A single study directly comparing nusinersen and risdiplam suggested no statistically significant differences between treatments but baseline imbalances in prognostic factors limit data comparability.

The MAA data suggested maintenance or improvement in motor function outcomes was common for both nusinersen and risdiplam separately across types 1, 2, and 3 SMA. Data for patient-reported outcomes measures (PROMs) was limited and showed mixed results for both treatments. However, maintenance or improvement was reported for some patient-reported scales for both nusinersen and risdiplam. Similarly, for both treatments separately, data for QoL was limited but suggested some improvement. Importantly, mortality rates in the MAA were low for both treatments and deaths appeared unrelated to treatments. Risdiplam data was more limited, reflecting its later availability through MAA.

The updated SLR for cost-effectiveness included 21 studies. The economic evaluations included comparisons between some or all the following SMA treatments: nusinersen; risdiplam; onasemnogene abeparvovec (OA); and standard of care/BSC. All studies adopted a Markov model with health states defined by functional motor milestones underpinning disease progression. Most quantified health benefits in quality-adjusted life years (QALYs) and life years gained (LYGs) and included cost-effectiveness evaluations with ICER as the outcome. Sources for health state utilities and costs, time horizon, modelling methods, outcomes, and involvement of patients and professionals all differed.

The EAG's base case cost-effectiveness analysis using the Biogen model showed that nusinersen [REDACTED] when compared with BSC. The scenario analysis indicated that nusinersen is likely [REDACTED] OA in treating presymptomatic and type 1 patients. The EAG's analysis using the Roche model showed that risdiplam was [REDACTED] when compared with BSC. However, risdiplam was [REDACTED]. In the scenario analysis, when equivalence in effectiveness was assumed between risdiplam and OA, risdiplam was [REDACTED] when treating the presymptomatic population, whereas it was [REDACTED] type 1 population.

Conclusions

The EAG's results mainly align with work from by the drug companies and by other international health agencies. There was some evidence that both nusinersen and risdiplam improved or stabilised motor function but there was mixed evidence for other outcomes. There was insufficient evidence to estimate the relative net health benefits of either treatment. Due to the limitations in the data for both nusinersen and risdiplam, the results should be viewed cautiously. Further research is required to strengthen the evidence base, particularly for outcomes considered important by professionals and patients.

2 Executive Summary

Background

Spinal muscular atrophy (SMA) is a rare, progressive neuromuscular disease most commonly caused by a genetic mutation in the survival motor neuron (SMN) gene on chromosome 5q. This genetic mutation causes gradual breakdown of motor neurons in the spinal cord and brainstem, leading to progressive muscle weakness, atrophy and, eventually, paralysis in late-stage disease. The condition affects muscles that involve crawling, walking, arm movement, head and neck movement, swallowing, and breathing. SMA is diagnosed through genetic testing and clinical examinations and has historically been categorised into types 0, 1, 2, 3, and 4 according to age of onset. The onset of neuromuscular weakness can range from birth to adulthood.

Currently, SMA is managed through multidisciplinary supportive care, which aims to minimise the impact of disability by addressing complications and improving quality of life. Care pathways have been developed for both paediatric and adult patients and the guidance informed by the international standard of care. The only treatment option currently recommended by the National Institute for Health and Care Excellence (NICE) is onasemnogene abeparvovec (OA; Zolgensma), a gene therapy. However, OA is only available for treating 5q SMA with a biallelic mutation in the SMN1 gene, either a) for presymptomatic babies aged 12 months and under with up to three copies of the SMN2 gene, or b) for type 1 babies who are not permanently ventilated or need tracheostomy and who are aged six months and under, or 7 to 12 months with agreement of the national multidisciplinary team.

There are two disease-modifying therapies that have been previously reviewed as NICE Single Technology Appraisals (STAs) and recommended for use under a Managed Access Agreement (MAA): nusinersen (Spinraza, Biogen) and risdiplam (Evrysdi, Roche). Nusinersen is a 2'-O-methoxyethyl antisense oligonucleotide administered by intrathecal injection. It stimulates the survival motor neuron-2 SMN2 gene to increase SMN protein levels. The intrathecal injection (12 mg/5 mL) requires an initial loading phase of four doses, with the first three doses taken at 14-day intervals and the fourth dose 30 days after the third dose. Maintenance doses are subsequently provided every four months. Risdiplam (Evrysdi, Roche) is a small-molecule survival motor neuron-2 (SMN2) gene splicing modifier which increases SMN protein levels in the central nervous system. It is administered orally through an oral syringe once per day.

Nusinersen and risdiplam were reviewed separately in TA588 and TA755 in 2019 and 2021, respectively, and both were recommended under an MAA with the instruction to collect further longer-term data. In this latest stage of a Multiple Technology Assessment (MTA), the Newcastle Evidence Assessment Group (EAG) were asked by NICE to assess the clinical and cost-effectiveness of both treatments for SMA.

Aims

This report describes the MTA investigating the clinical and cost effectiveness of nusinersen and risdiplam as treatments for SMA.

Structure of the report and justification of approach

This MTA was undertaken following two previous appraisals of the individual technologies (TA588 and TA755) and subsequent MAAs in each case. This is a condition in which the

available data from clinical trials is acknowledged to not be fully reflective of the lived experience of patients and carers and where considerable uncertainties were identified in the original appraisals. To reflect this, the EAG have undertaken work to analyse quantitative and qualitative data available from the MAA. In addition, the EAG have undertaken qualitative analysis of data from patient submissions and from meetings with representatives of professional organisations and patient groups, as well as free-text data provided by both adult and paediatric registries. These analyses are presented in addition to the critiques of the submissions from Biogen and Roche, updated systematic literature reviews of clinical and cost effectiveness evidence, and economic modelling. The qualitative analyses should be considered both individually and as providing essential context to the systematic reviews and models.

Methods

Throughout the MTA process, the EAG consulted with both Biogen and Roche, professional organisations, clinicians, and representatives of patient organisations. Three meetings each were held with Biogen, Roche, professional and patient organisations to discuss the EAG's approach to the qualitative analysis, clinical SLR, and economic modelling, as well as to discuss preliminary results. These meetings included representation from NICE. Individual clinicians were also consulted to provide further, condition-specific context and validation for the methods used by the EAG. The discussions from all meetings helped to shape the approach of the EAG to the MTA, including report structure, inclusion of additional outcomes and the approach to the economic modelling.

Critique of the company submissions

The EAG reviewed and critically appraised the clinical evidence and economic models submitted by the companies, as well as additional information in response to points for clarification requested by the EAG. The EAG critiqued the submitted clinical effectiveness evidence, economic model structures and the economic evidence used to parameterise the economic models for each of the population groups, which was then summarised within the report.

Qualitative analysis

The EAG conducted qualitative framework analyses to identify areas of key concern surrounding living with SMA, as well as surrounding the potential benefits of nusinersen and risdiplam from the perspective of those with a lived experience of SMA. Several sources were used to inform the qualitative analysis, including: transcripts of meetings between the EAG and both professional and patient organisations; patient and professional organisation submissions to NICE; professional and patient expert submissions to NICE; case studies and quotations included as part of an appendix to the submission to NICE provided by SMA UK, Muscular Dystrophy UK and SMA Reach UK; and free-text data provided to the EAG about both paediatric and adult populations from SMA REACH UK.

A framework analysis was undertaken, focusing on identifying the issues of most importance to people with a lived experience of SMA, as well as the impacts of treatment with nusinersen and risdiplam. The EAG developed the coding framework based on the decision problem and discussions with patient and professional organisations. Two members of the EAG iteratively developed the final framework, which was transferred to the software Nvivo for coding. Two members of the EAG undertook two pilot coding phases to establish concordance between coders and identify areas where the coding framework could be modified. Following this, most

of the sources were coded by a single EAG researcher and checked by a second. Any potentially missing or erroneous codes identified by the second researcher were discussed and agreed prior to analysis.

The coded data were interrogated to identify key subthemes from the framework inductively. Following initial discussion of the methods and coding with professional and patient organisations, both researchers wrote narratives surrounding the major themes and sub-themes identified from the coding phase, including illustrative quotations where appropriate. The narratives were written from a pragmatic perspective to present the findings of the qualitative data without additional theory generation or interpretation. This step was repeated when free-text data from the registry was received. Once written, researchers read the narratives alongside the original coding to ensure there were no potentially missing sub-themes, that they were written from the pragmatic standpoint, and that the narratives and direct quotations used were adequately contextualised insofar as possible.

SLR of clinical effectiveness

Searches from the original review¹ were updated in March 2025 to incorporate newly published records meeting the eligibility criteria. The search results were screened in duplicate, along with the list of excluded studies from the original review, to identify new evidence, including from conference abstracts which were excluded from the earlier review. Data were extracted into a data extraction form created in Excel, which had been piloted and refined to capture all the data required for the synthesis. For the review update the EAG extracted data where possible on some additional outcomes identified as important by the patient and professional groups. Randomised controlled trials (RCTs) and non-randomised controlled studies were critically appraised using the Risk of Bias v2 (RoB v2) and Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tools, respectively. The results were narratively synthesised according to the following hierarchy: drug (nusinersen or risdiplam); outcome type (e.g. motor outcomes); outcome measure (e.g. CHOP INTEND); and SMA type. Newly included data is identified within the review.

Managed Access Agreement (MAA)

The EAG critically assessed the MAA reports for both nusinersen and risdiplam; in some instances, data were updated for outcomes in both the paediatric and adult registries for both treatments. The analyses for nusinersen and risdiplam were sometimes limited due to small sample sizes, especially at later time points. However, the registries noted these limitations and the EAG agreed with the way in which data was analysed. Motor outcomes with enough data were analysed using mixed models for repeated measures (MMRM), while other outcomes (e.g. patient-reported outcomes) were presented using descriptive statistics.

SLR of economic evidence

Searches from the original review were updated in March 2025 to incorporate newly published records meeting the eligibility criteria. Data were extracted into a data extraction form created in Excel, which had been piloted and refined to capture all the data required for the synthesis. In line with the original review, the critical appraisal strategy involved assessing all included economic evaluations using the Consolidated Health Economic Evaluation Reporting Standard (CHEERS) 2022 checklist, as well as appraising records against the Philips' checklist. Each record was assessed by one reviewer and checked by a second reviewer, with any disagreements being resolved by discussion or consultation with a third reviewer. The evidence identified on modelling techniques, structures and inputs (including clinical, survival

analysis methods, resource use and costs, utility estimates) that were required to generate the models, assumptions and key outcomes were summarised. Any key issues that should be considered in model-based economic analyses conducted in the future were also summarised.

Economic modelling

The EAG conducted its own economic analyses, drawing on the evidence and models submitted by both companies. Because of the differences in population characteristics for nusinersen and risdiplam treatments, the treatments were evaluated using separate models (adapted versions of Biogen and Roche models separately for each SMA type). However, efforts were made to align the analyses for consistency and to address the key uncertainties surrounding the cost-effectiveness of the relevant disease-modifying therapies within the context of the decision problem.

In the base-case analyses, the EAG used adapted Biogen and Roche models to compare nusinersen versus BSC, and risdiplam versus BSC, respectively, across presymptomatic, type 1, and type 2/3 SMA populations.

For the Biogen (nusinersen) model, the EAG's base-case did not include carer utility, which had been incorporated in the company model. Instead the EAG explored the impact of carer utility through scenario analysis. Several additional scenarios were conducted to explore the impact of uncertainty in the parameters, including a comparison between nusinersen and OA, with and without assuming equivalence between the treatments.

For the Roche (risdiplam) model, the EAG's base-case also excluded carer utility and aligned key parameters such as time horizons, health state utility values, and healthcare resource use with those used in the Biogen (nusinersen) model. Additional scenario analyses were conducted comparing risdiplam vs nusinersen, and risdiplam vs OA, with and without assuming equivalence, alongside various other scenarios exploring the impact of uncertainty in the cost and utility parameters.

Results: key findings

Critique of company submissions

A critique of the indirect treatment comparisons (ITCs) was conducted for both company submissions (nusinersen – Biogen; risdiplam – Roche). Biogen used matching-adjusted indirect comparisons (MAICs) to compare nusinersen to either OA or risdiplam. If a MAIC was still deemed unfeasible, a simulated treatment comparison (STC) was implemented. Biogen noted that the amount of bias (systematic error) in these estimates is unknown, likely to be substantial, and could even exceed the magnitude of treatment effects being estimated. Fourteen analyses were conducted by Biogen (seven comparing to OA and seven comparing to risdiplam). For both comparisons there was a common issue of the effective sample size (ESS) being below 30, with some less than 10. These small ESS suggest a potential for high variability between the populations being compared, meaning the estimate may be unstable. When a MAIC was deemed unfeasible, an STC was used with non-linear data (i.e. for the Hammersmith Functional Motor Scale Expanded (HFMSE) and Revised Upper Limb Module (RULM) motor outcomes when comparing to risdiplam). This is commonly the case in SMA, where it is possible to show improvements, maintenance or deterioration over time, so results can be open to bias. Specifically, as the results are generated via a linear regression model using individual patient data (IPD) from one trial compared to aggregate data from the

comparator trial, the non-linearity assumption may be violated. If there is non-linearity substituting the mean covariate values from the comparator trial into the regression, this can lead to biased estimates due to issues between the relationship of the mean of the outcome and the mean of the covariates.

Roche also used MAICs or STCs depending on feasibility. Eighteen analyses were conducted by Roche (12 comparing risdiplam to nusinersen and six comparing to OA). The same issue of non-linearity for STCs is present in these analyses as in the aforementioned nusinersen (Biogen) analyses. For example, risdiplam vs OA in type 1 patients utilises an STC. When comparing risdiplam to nusinersen in unanchored MAICs, the ESS was above 35, meaning there was a potential for less bias and uncertainty in the results. In type 2/3 patients, Roche conducted an anchored MAIC, which was not conducted by Biogen. Doing this required the assumption that the placebo and sham arms were comparable, which may not be the case. The lack of comparability between the placebo and sham arms is supported by a reduced ESS of less than 10 in the comparator arm. Additionally, the ESS in the intervention arm was less than 30. The company highlighted this as a limitation and mentioned the increased uncertainty of the relative effects. There are inherent differences between the populations who are eligible for each treatment, with the reduced ESS mainly driven by age. Additionally, the severity of deterioration in those receiving risdiplam at baseline was usually higher than that of patients receiving nusinersen. Therefore, such anchored comparisons should be interpreted with caution.

Overall, both companies attempted to make the analyses possible and plausible with the data available. Concerns about sample sizes and naïve analysis are warranted. However, this is mainly driven by availability of data in a rare disease.

The economic model structures used by the companies were appropriate conceptualisations of the decision problem and disease progression. However, important differences in patient characteristics and the clinical definitions of motor milestones made it difficult to compare the effectiveness of therapies across models. This limitation also affected the interpretation of results from the MAA, further reducing their applicability to the cost-effectiveness models. Beyond the limitations arising from differences in clinical outcome measures, the quality of relative effectiveness data available for ITCs further restricted the EAG's ability to assess the relative effectiveness of disease-modifying therapies in the company's base-case models. As a result, these comparisons had to be explored through scenario analyses. Patient health-related quality of life (HRQoL) was a major source of uncertainty in both submissions, largely due to the challenges of measuring HRQoL in children and the rarity and severity of the disease. The greatest uncertainty stemmed from QoL estimates associated with severe health states, such as permanent ventilation, non-sitting and sitting-related states. The EAG acknowledges that the perspective of informal carers is an important consideration in this disease area, and that NICE guidelines permit the inclusion of carer health-related quality of life (HRQoL) in appraisals. However, the two company submissions adopted markedly different approaches to incorporating informal carer HRQoL, relying on data elicited outside the clinical trials.

Another major source of uncertainty in the cost-effectiveness analysis across both company submissions was the estimation of disease-related costs for the most severe health states, including permanent ventilation, non-sitting and sitting-related states. At these levels of severity, the cost of care can be close to the maximum willingness-to-pay threshold of the healthcare system. As a result, any treatment that increases costs, regardless of its

effectiveness, risks exceeding this willingness to pay threshold. The EAG identified substantial variation in cost estimates for the model health states, driven by a lack of robust data.

Overall, in presymptomatic patients, both risdiplam and nusinersen had the potential to improve motor milestones to the least severe levels of the disease and reduce the risk of permanent ventilation. However, the evidence was insufficient to draw strong conclusions compared to BSC. For type 1 patients, both treatments appeared to reduce the risk of permanent ventilation and maintain motor function around sitting-related health states, although significant evidence gaps remained for risdiplam. In patients with type 2 and 3 SMA, there was stronger evidence that both treatments helped maintain motor milestones related to sitting when compared to BSC. These findings have important implications for the economic analysis, as the costs of care in sitting-related health states are substantial and must be weighed against gains in patient quality of life. However, this also constrains the analysis to motor milestones measured by instruments that may lack sensitivity to fully capture the disease's complexity. For this reason the context provided by qualitative data should be considered alongside the results of the modelling.

Qualitative analysis

The EAG's qualitative analysis highlighted the experiences of those living with SMA and their carers, including their experiences of treatment. The analysis covered themes related to NICE's decision problem, as well as themes that were raised as important by patient and professional organisations in discussion with the EAG and within the wider literature. These included: ability to socialise; activities of daily living; impact on ability to socialise; impact on education; impact on families and carers; independence; patient choice; psychological impact; and the "spectrum" of SMA (whereby two people with the same SMA type may have very different functional abilities and life experiences).

The qualitative analysis emphasised the great impacts of SMA on people's motor, bulbar and respiratory functions, as well as the impact SMA had on their overall quality of life. With regards to respiratory function, people also often highlighted a link between respiratory infections and hospitalisation. The analysis also emphasised that SMA impacts people's ability to do daily activities (such as eating, washing and putting on clothes), their ability to socialise with other people, and that SMA had a psychological impact on people with SMA, those who care for them and their wider personal networks. People also discussed the economic implications of SMA, including the personal financial burden of needing to buy new equipment (e.g. wheelchairs) or travelling to medical appointments.

People's experiences of nusinersen and risdiplam were also explored. Although there were occasional reports to the contrary, the qualitative analysis suggested that both treatments have a positive impact on people with SMA, particularly with regards to maintaining or improving the condition. However, it was often not clear what treatments the people in the analyses were taking, making it challenging to find out more about what effect each of the treatments separately had on the lives of people with SMA and their carers.

Crucially, when the EAG spoke to clinicians and representatives of patient organisations, they stated that the current ways in which some outcomes are measured, such as motor function, were not currently sensitive enough to be able to capture what people with SMA and their families consider to be meaningful changes in their own abilities. Furthermore, the importance of maintaining function was emphasised as being just as meaningful and important to patients as improvements in their overall condition. Additionally, they highlighted

that outcomes such as bulbar function and fatigue were particularly important functional outcomes to patients and their families and carers but that these were not well captured within the current evidence base.

It should be noted that the qualitative analysis had several limitations, including the use of framework analysis, which was appropriate for the timescale of the project but meant that a deeper exploration of the data through thematic analysis was not undertaken. Some of the data provided across the submissions often had few details about the demographics of those who contributed (e.g. SMA type) or what treatment they had been administered. This made it challenging in some cases to be able to connect peoples' experiences, particularly of treatment effects, with either nusinersen or risdiplam. Furthermore, there were caveats surrounding the registry data provided to the EAG. The data from the adult registry lacked detailed demographic information, meaning it was not possible to include details such as adults' SMA type, functional status or age at diagnosis. The registries also noted in discussion with the EAG that those providing free-text data for the paediatric registry were not always the primary caregiver for the child. As it was not possible to note when this was the case, the EAG were unable to provide this context in the report. Finally, the EAG originally aimed to weave the results of the qualitative analysis throughout the report but, due to these constraints relating to structure and the nature of the data, this was not possible.

Clinical effectiveness SLR

The total number of records included in the SLR was 147. Of these, 130 assessed nusinersen (of which 22 were new in the update), comprising three RCTs, eight controlled studies and 119 single arm studies; 13 assessed risdiplam (of which three were new), including one RCT and 12 were single arm studies); four administered both nusinersen and risdiplam (of which three were new), including one non-randomised controlled study and three single arm studies; 20 were ongoing trials. Risk of bias was assessed using the RoB v2 for RCTs and the ROBINS-I v2 for non-randomised controlled studies. Potential sources of bias were identified in all studies assessed, with no studies rated as having low risk of bias overall. For nusinersen, the three RCTs were rated as 'some concerns' overall. Nine non-randomised, controlled studies were rated as 'moderate' risk of bias and 15 were rated as 'serious' risk of bias. For risdiplam, one RCT was rated as 'some concerns' on its overall risk of bias assessment. For the comparison between nusinersen and risdiplam, one non-randomised controlled study was rated as 'serious' risk of bias overall. The quality of single-arm studies was not assessed due to the timelines and volume of included evidence, which is consistent with the approach taken in the earlier review. No evidence was identified assessing the effectiveness of nusinersen or risdiplam in patients with types 0 and 4 SMA. As highlighted by some submissions within the qualitative analysis, this may present an equality issue for these patients.

For the effects of nusinersen on motor outcomes, the evidence suggests improved or maintained motor function on average across the spectrum of SMA types included for each of the outcomes assessed, relative to a control group of before-after observations, for follow-up timepoints of up to five years. Some studies reported differences in effectiveness between population subgroups in relation to age and SMA type. Favourable results were also reported in relation to mortality, with higher survival rates amongst nusinersen-treated patients overall. The long-term safety profile of nusinersen was found to be favourable. Stability or maintenance in respiratory function was generally suggested. Mixed results were reported regarding the effects on bulbar function and quality of life of carers and SMA patients.

For risdiplam, patients continued to improve or maintain their motor function in all measures for all SMA types included. There was mixed evidence for the effects of risdiplam on bulbar function and ventilation. Evidence suggested maintenance or small increases or decreases in respiratory function, although the evidence was sparse. Due to the lack of controlled studies, the evidence on mortality was limited by the inability to compare longevity between people who were and were not treated with risdiplam but survival for type 1 patients was higher than in untreated populations. Adverse effects were generally not serious.

From the limited evidence available, nusinersen and risdiplam appeared to have comparable efficacy, although study limitations (e.g. baseline imbalances in prognostic factors) undermine the comparability of the data.

Managed Access Agreement (MAA)

The results of both the nusinersen and risdiplam MAAs separately suggested maintenance or improvement, mostly for motor outcomes, across all types assessed. From the paediatric registry, nusinersen had longer follow-up data available than risdiplam for motor outcomes (~4+ years vs ~1.5+ years, respectively). While the adult registry for risdiplam extended to ~4 years, the patient numbers were smaller at this point than those in the nusinersen MAA. This is to be expected given the timeline of when each drug was made available, with nusinersen being made available first. Data for patient-reported outcome measures was lacking for both treatments and suggested some varying results. However, maintenance or improvement was reported for some scales for both nusinersen and risdiplam. Similarly, for both treatments separately, data surrounding QoL were also lacking but did suggest some improvement. Importantly, mortality rates in the MAA were generally low for both treatments and deaths that did occur appeared to be unrelated to the treatments.

SLR of economic evidence

The updated SLR of economic evidence included 21 studies. All the included studies from the SLR undertook economic evaluation of SMA treatments. The studies varied based on the patient population, interventions and comparators, outcome measures, modelling methods adopted, resource use and costs, health-state utility estimates, time horizons, analyses, assumptions and limitations, and patient and professional engagements. SMA types 1, 2 and/or 3 were considered in most of the studies, with some using subgroup analysis based on age and disease characteristics.

There was a consensus in the type of model adopted for cost-effectiveness evaluation, with the studies using Markov models for estimating the SMA treatment effectiveness. There was a need for generating robust and reliable data on long-term follow-up and real-world evidence on treatment efficacy that could enhance the accuracy of evaluation and improve the decision-making on SMA treatments. There were significant variations in sources and methods used for utility estimates among different studies, due to a lack of consensus around the best source and methods that could be used to elicit the utility estimates. The resource use quantification and subsequent cost estimation was influenced by variations in data sources, age-adjusted cost estimates, assumptions in treatment modelling, definitions of BSC or standard of care, and other complexities and heterogeneity around SMA treatment modelling assumptions, resulting in the cost-effectiveness results across the studies being unsuitable for comparison. It would be difficult to draw conclusions to inform SMA treatment modelling choices from the results of the SLR. But these studies could be used to analyse the impact of different data sources, methods and assumptions in modelling SMA treatments. The assessment of cost-

effectiveness SLR results indicates a need for robust and reliable data on treatment effectiveness, real-world evidence generation of utility estimates and consensus in adopting resource use and estimating costs for SMA treatment evaluation.

Economic modelling

The EAG's cost-effectiveness analysis, using the Biogen model, indicated that [REDACTED] for the treatment of presymptomatic SMA population when compared with the BSC. For type 1 and type 2/3 SMA populations, [REDACTED] at NICE's willingness pay threshold of £30,000 per QALY. Given the limitations in the available evidence, nusinersen is also [REDACTED] than OA in the treatment of both presymptomatic and type 1 populations.

The EAG's cost-effectiveness analysis, using the Roche model, indicated that risdiplam [REDACTED] for the treatment of presymptomatic, type 1 or type 2/3 SMA populations when compared with BSC. [REDACTED]
[REDACTED]
[REDACTED] When effectiveness equivalence was assumed between risdiplam and OA, [REDACTED].

Our conclusions on cost-effectiveness of nusinersen and risdiplam are broadly consistent with those reported in the company submissions and by other international HTA bodies. However, these results are largely based on limited evidence and should be interpreted with caution. In the absence of robust comparative data, there remains insufficient evidence to reliably estimate the relative net health benefits of risdiplam, nusinersen or OA in patients with SMA. Therefore, there is a clear and continued need for further evidence to minimise the uncertainty in the cost-effectiveness analysis of these treatments for SMA.

Key issues identified by the EAG

The EAG identified several issues during the MTA report process that may introduce uncertainties into the clinical and cost-effectiveness results. These are summarised in the table below.

Issue	Summary
Comparability of the patients receiving nusinersen or risdiplam	What is the issue: There are notable differences in the eligibility criteria between nusinersen and risdiplam. For example, nusinersen is an intrathecal injection which requires spinal access, and spine deformities can lead to difficulties implementing the treatment. These differences in eligibility lead to some patients not being able to receive one treatment who may be eligible for another. Additionally, patients receiving risdiplam were generally more severe than those who were treated with nusinersen. Why this is considered important: The issues of comparability of the two treatment patient groups leads to uncertainty in the ITC analyses from the company submissions. These patient differences led to the EAG considering the two treatments separately. Therefore, both treatments are reviewed separately to each other and then some discussion about general themes between the two treatments are discussed. There is also very little clinical evidence directly comparing the two treatments. As a consequence, the economic modelling was undertaken for the two treatments separately in presymptomatic, type 1, and type 2/3 for both nusinersen (Biogen model) and risdiplam (Roche model).
Insensitivity of tools to assess motor function to capture improvements considered important by patients, families and their carers	What is the issue: The tools used to measure motor function generally lack the granularity to capture improvements in motor function that patients, carers, and clinicians may deem important. This issue was emphasised by both professionals and representatives of patient organisations in discussion with the EAG throughout the MTA process. There is also a focus on gross motor skills within the evidence base (e.g. crawling, sitting), whereas fine motor skills such as being able to move the hand towards an object (e.g. wheelchair control) are not captured and these are considered crucial skills to be maintained. Why this is considered important: The utility scores used for each model's health states may inadequately capture nuanced motor improvements from treatments that are meaningful to SMA patients, as well as their families and carers (e.g. lifting the head, being able to hold something, or even being able to sit independently for a few seconds). A utility increment of 0.1 has been assumed and incorporated into the economic model to account for these nuanced improvements from treatments not adequately being captured. However, the EAG caution that this utility increment may not correctly reflect these improvements but would give indicative results from the consideration of additional utility gains.
Lack of data for bulbar function, non-ventilatory respiratory support and scoliosis, which impacts clinical conclusions and leads to inability to incorporate utility and	What is the issue: The clinical effectiveness evidence of the treatments on outcomes such as bulbar function was lacking. Patients, carers, and professionals highlighted these as key outcomes for improving quality of life when meeting with the EAG. However, it is difficult to make meaningful conclusions due to lack of data for these outcomes.

Issue	Summary
cost impacts of in the economic models	Why this is considered important: The EAG's base-case models did not explicitly incorporate the utility and cost impacts of bulbar function, non-ventilatory respiratory support and scoliosis separately. These impacts were assumed to be captured within the HSUVs and associated resource utilisation costs. The EAG was concerned that including these elements separately could result in double counting and therefore over-estimating their impact on cost-effectiveness. However, based on input from the clinical experts and patient organisations, the EAG recognises the particular importance of maintaining or improving bulbar function for people with SMA. In response, the EAG conducted a scenario analysis within the type 2/3 models, incorporating both utility decrement and additional healthcare costs associated with bulbar function. Due to a lack of relevant data, it was not possible to model the impact of bulbar function for presymptomatic or type 1 populations. Even within the type 2/3 model, the data used to inform the bulbar dysfunction were limited and several assumptions were required. Therefore, the results of this scenario analysis should be interpreted with caution.
Lack of data for outcomes considered most important by patients	What is the issue: In discussion with the EAG and from the qualitative analyses, bulbar function, and stamina and fatigue were outcomes within the NICE decision problem that were considered important by professionals, patients, and carers. Furthermore, several outcomes not included within the decision problem were also considered to be important, including activities of daily living; ability to socialise; independence; impact on carers and families; and the impact on education and work. The EAG added the outcomes considered important by stakeholders into the data extraction form for the update to the clinical SLR, as well as those included within the decision problem. However, for most of these outcomes, data were lacking for both nusinersen and risdiplam. Why this is considered important: Although the EAG attempted to identify evidence surrounding outcomes that patients and professionals stated are important, there is currently a lack of evidence surrounding bulbar function, and stamina and fatigue, meaning the EAG's ability to draw any conclusions surrounding these outcomes is limited. The impact of the lack of data surrounding bulbar function on the economic models has already been identified as a key issue.
No data for type 0 or 4 SMA	What is the issue: The EAG did not identify any evidence surrounding the effectiveness or cost-effectiveness of nusinersen or risdiplam in patients with SMA types 0 and 4. Why this is considered important: Patients with either type 0 or type 4 SMA are not represented within the clinical and cost-effectiveness sections of this report due to the lack of data. Representatives of patient organisations highlighted to the EAG that the lack of access to the MAA for adults with type 4 SMA is a potential equality issue.
Patient heterogeneity	What is the issue: Even within individual functional states (e.g. sitters), there is a large range of heterogeneity in terms

Issue	Summary
	of capabilities and care requirements. The qualitative analysis and discussion between professional and patient organisations with the EAG highlighted this heterogeneity within SMA, emphasising differences in the trajectory of the condition, even between individuals with the same SMA type and SMN2 copy numbers. Why this is considered important: The modelling the EAG were able to undertake is based on the functional states and was not able to capture the granularity of changes within those states which may be more important to individual patients than transitions between states. There is therefore uncertainty about the extent to which the maintenance or improvement of function is adequately captured.
Lack of controlled trials for presymptomatic patients	What is the issue: There are no controlled studies that include any therapy for presymptomatic patients. Risdiplam also lacked controlled studies for type 1 patients. Why this is considered important: The lack of data means that the evidence for this population is more uncertain.
Effectiveness data from single-arm trials used to inform the economic models	What is the issue: The effectiveness data (e.g. transitions, relative effect, decline in health states) used in the cost-effectiveness models largely come from single arm trials in the absence of RCTs. Why this is considered important: Whilst it may not always be feasible or ethical to conduct a RCT for treatments in rare diseases like 5q SMA, it therefore becomes necessary to use the effectiveness data coming from single arm trials. Using evidence from single arm trials may introduce bias in favour of the treatments under evaluation.
Heterogeneity in the motor milestones used to define disease progression in the model	What is the issue: The motor milestone scores used in defining disease progression in terms of model health states are derived from different tools which vary in their scoring system. Why this is considered important: The EAG note that assuming equivalence of health states defined by tools varying in their scoring system may add further uncertainty in motor functions, patient health states, and ultimately in the cost-effectiveness outcomes due to the sensitivity in how well the tools capture the true impact of the disease as valued by patients and carers.
Lack of data to be able to incorporate carer utility increments into the base-case economic models	What is the issue: The impact on families and carers for those living with SMA was highlighted as being important both in discussions between the EAG and patient organisations and the qualitative analyses. However, carer utility increments have not been incorporated in the EAG base-case models due to concerns around the methodological approach, the number of assumptions required to incorporate carer utilities, and the robustness of the available evidence to allow this. Why this is considered important: Exclusion of carer utility gains/losses from the EAG base-case models may undermine the full value of treatments. However, the impact of incorporating carer utility in the cost-effectiveness results was explored in the scenario analyses to determine the potential

Issue	Summary
	impact on cost-effectiveness and can be incorporated into decision making.
Data surrounding discontinuation of treatment only available for nusinersen	What is the issue: Discontinuation from treatments were informed by the MAA data but were only incorporated into the Biogen model for nusinersen. Roche did not account for treatment discontinuation in their economic model, reasoning that discontinuation from risdiplam was unlikely in clinical practice - a justification based on the trial data, REACH data, and clinical expert feedback. Why this is considered important: Not incorporating treatment discontinuation in the Roche models may favour risdiplam as the EAG's discussions with clinical experts suggested that people may discontinue or switch from risdiplam due to known adverse events, such as potential effects on fertility. The EAG also notes that the discontinuation data used in the models were based on short-term MAA follow-up, which may overestimate the sustained benefits from treatment over the patient's lifetime. In addition, discontinuation from nusinersen incorporated into the Biogen (nusinersen) model assume that patients discontinuing treatments would go on to receive BSC, accruing the costs and outcomes of BSC after discontinuation. However, in clinical practice, those discontinuing may switch to alternative DMTs rather than BSC alone. Due to the lack of robust evidence, the potential impact of treatment switching could not be modelled. Therefore, the EAG caution that assumptions surrounding treatment discontinuations may introduce additional uncertainty into the cost-effectiveness results.
Uncertainty in patient utilities for severe health states	What is the issue: The EAG found large variation in the utility values used to calculate health-related quality of life for patients across the previous technology appraisals for nusinersen, risdiplam and OA (TA588, TA755, HST24). Why is this considered important: DMTs have a larger impact on patients at the more severe stages of the disease or when patients are unable to stand with or without support. Therefore, the size of the benefit in the economic assessment is directly linked with these estimates. Furthermore, as this relates to the most severe stages of the disease, with some values considered close to equivalence or worse than being in the "dead" health state, it is important that they reflect patient preferences appropriately.
Uncertainty in patient costs for severe health states	What is the issue: The EAG found large variation in the disease-related cost values for the more severe health states, particularly for patients who are unable to stand with or without support. Why is this considered important: The level of health care costs becomes considerably higher at the highest levels of severity of the disease or the lower levels of motor function (not yet standing with or without support). These estimates were crucial in defining whether the introduction of a new DMT into the disease pathway was cost-effective, yet evidence in this area was scarce.

Issue	Summary
	Abbreviations: BSC = best supportive care; DMTs = disease modifying therapy; EAG = Evidence Assessment Group; HSUV = health state utility value; MAA = Managed Access Agreement; MAIC = matching-adjusted indirect comparison; OA = onasemnogene abeparvovec; RCT = randomised controlled trial; SLR = systematic literature review; SMA = spinal muscular atrophy; SMN2 = survival motor neuron 2.

Conclusions and recommendations for further research

For both nusinersen and risdiplam, there was evidence of maintenance or improvement in motor functions. Maintenance was considered an important outcome by professionals and patient organisations. Data on other outcomes, such as quality of life, showed mixed results for both treatments. The cost-effectiveness studies included in the updated SLR were heterogenous. The SLRs indicate a need for robust and reliable data on treatment effectiveness, real-world evidence generation of utility estimates and consensus in adopting resource use and estimating costs for SMA treatment evaluation. The findings of the EAG's cost-effectiveness analysis were comparable to those reported in the original technology appraisals of nusinersen (TA588) and risdiplam (TA755).

The previous technology assessments highlighted a lack of longitudinal and comparative data for both nusinersen and risdiplam. This has been partially addressed by longer follow-up periods of the clinical trials (~8 years for nusinersen and 5 years for risdiplam), and use of an MAA for some outcomes, mainly motor function. However, the lack of a comparative clinical trial comparing type 1 patients receiving risdiplam to treatment-naïve patients, noted in the original technology assessment for risdiplam has not been addressed. Direct comparative evidence between the two treatments and OA is also lacking. However, differences in populations eligible for the treatments make direct comparisons challenging. Furthermore, the qualitative analysis highlighted that treatments may have an impact on fine motor skills that are not well captured by the current tools used to measure motor function across SMA types.

The cost-effectiveness results are based on limited evidence and should be interpreted as such. In the absence of comparative data, the EAG concludes that there is insufficient evidence to estimate the relative net health benefits of risdiplam or nusinersen in patients with SMA. Therefore, there is a clear and continued need for further evidence to minimise the uncertainty in the cost-effectiveness analysis of these treatments for SMA. Future research should also aim to collect data highlighted as important by patient groups (e.g. activities of daily living, stamina and fatigue).

3 Plain English Summary

Background

Spinal muscular atrophy (SMA) is a rare genetic condition that causes muscle weakness and wasting away over time. There are five types of SMA: Type 0, where the condition begins before birth; type 1, which starts in babies less than six months old; type 2, which starts in babies and toddlers aged 6 to 17 months; type 3, which starts in children and teenagers from 18 months to 17 years old; and type 4, which starts in adulthood. SMA can affect people very differently but common symptoms people with SMA may experience include muscle weakness, movement problems and problems with breathing and swallowing. Without treatment children with type 1 SMA are likely to die in infancy. SMA has a considerable effect on the quality of life of people with the condition, caregivers and their families. People with SMA often require continual support from others, which can involve full-time care and attention. This kind of support is physically demanding but can also greatly impact on the mental health and wellbeing of people with SMA, their families and carers.

Currently, there is only one treatment for SMA recommended for use within the National Health Service (NHS), a gene therapy called onasemnogene abeparvovec (OA). OA is available for treating 5q SMA with a biallelic mutation in the SMN1 gene, either a) for presymptomatic babies aged 12 months and under with up to three copies of the SMN2 gene, or b) for type 1 babies who are not permanently ventilated or need tracheostomy and who are aged six months and under, or 7 to 12 months with agreement of the national multidisciplinary team. However, there are two other treatments, nusinersen and risdiplam, that are available to people with SMA under strict criteria as part of a Managed Access Agreement (MAA). Nusinersen is delivered by a spinal injection (a lumbar puncture) every four months. Risdiplam is a medication that is taken orally every day. Both nusinersen and risdiplam have each been previously assessed separately in a process known as a Single Technology Appraisal (STA). Both these STAs found uncertainties about the data available at the time they were produced.

The Evidence Assessment Group (EAG) at Newcastle University were asked by NICE to consider the evidence for nusinersen and risdiplam in an assessment called a Multiple Technology Appraisal (MTA). The EAG does not decide whether nusinersen and risdiplam will be recommended; NICE will decide if these treatments are recommended for wider use within the NHS. The aim of the EAG's report is to help the NICE Committee in their decision-making process on whether these treatments should be approved for use within the NHS.

How the EAG assessed the technologies

The EAG had three discussions each with clinicians and representatives of patient groups to shape the methods and talk about some of the results. The EAG also consulted with other clinical advisors in online meetings and had meetings with the two companies who make the treatments throughout the process of developing the report.

The EAG did not compare nusinersen and risdiplam directly within the report. This is because the EAG believed that the people who receive nusinersen and risdiplam are too different to be able to compare how well each of the treatments works.

The EAG were provided with reports about nusinersen and risdiplam from the companies who make the treatments. These reports contained information about how well both nusinersen and risdiplam might work for treating SMA, as well as if they may be considered good value

for money for the NHS. The EAG read the submissions from both companies to see how robust the evidence they provided was before highlighting any uncertainties in this MTA report.

The EAG included qualitative information about peoples' experiences of SMA and treatments for SMA, as well as the perspectives of professional and patient organisations. The outcome measures considered important by representatives of professional and patient organisations, as well as those requested by NICE in their overall scope for the work, became the themes for the qualitative analysis. The findings from the qualitative analysis were included in this MTA report to help contextualise the findings with lived experiences of SMA and having treatment.

The EAG also brought all the relevant clinical evidence about nusinersen and risdiplam together in a process called an evidence synthesis to find out more about how well the treatments work for different SMA types. This was done by building on work a previous report from another EAG and adding in new information. The EAG also received data from the MAA about both nusinersen and risdiplam. These data were also analysed by the EAG to find out more about how well both nusinersen and risdiplam work in real life.

The EAG studied all the relevant evidence related to cost-effectiveness analyses in studies about SMA treatments. New evidence was added to the initial evidence from the previous report. The information from this evidence was collected and studied to understand more about the health benefits, costs, and other factors which were considered in the economic modelling of treatments for SMA.

Finally, the EAG adapted existing separate economic models to find out how cost-effective nusinersen and risdiplam are. The two main economic models assessed how cost-effective nusinersen and risdiplam each were when compared with best supportive care (BSC). The EAG also created exploratory economic models to assess the cost-effectiveness of the following comparisons: nusinersen compared with risdiplam; nusinersen compared with OA; and risdiplam compared with OA. A separate economic model was created for each type of SMA, as long as there were enough data available for individual SMA types.

Main results of the MTA

The EAG's qualitative analysis highlighted the experiences of those living with SMA and their carers, including their experiences of treatment. The analysis further emphasised the major impacts of SMA on people's ability to move, swallow, and breathe, and on their overall quality of life. They also stated that SMA impacted their ability to do daily activities (such as eating, washing and putting on clothes), their ability to socialise with other people, and that SMA had a psychological impact on people with SMA, those who care for them and their wider personal networks. Their experiences of having nusinersen and risdiplam were also explored, but it was often not clear what treatments the people in the analyses were taking, making it challenging to find out more about what effect each of the treatments had on the lives of people with SMA and their carers.

Additionally, when the EAG spoke to clinicians, including specialist physiotherapists, and representatives of patient organisations, they said that the current ways in which some outcomes are measured, such as someone's ability to move, were not sensitive enough to be able to capture what people with SMA and their families consider to be meaningful changes in their own abilities and lives. They also said that there were outcome measures important to patients and their families, such as bulbar function (which affects someone's ability to swallow and breathe) and fatigue, that are not well reported in the evidence we currently have.

When looking at the clinical evidence that both companies submitted to NICE, the EAG found that there were concerns around how many people were included in the statistical analyses but that both companies tried to make the analyses possible with the data they had available. When looking at the evidence on nusinersen and risdiplam separately in their evidence synthesis, the EAG added new information to what had already been done previously as well as adding information from sources such as conference abstracts. There was more data about nusinersen than risdiplam, but this is expected because nusinersen has been available for a longer time. The EAG found that, generally, nusinersen and risdiplam both either maintained or improved motor functions for people with SMA types 1, 2 and 3. There were more mixed results from the data about how much nusinersen and risdiplam impact on bulbar function and people's quality of life. More people who received nusinersen survived for longer, but there was less information about survival for people taking risdiplam. However, for both treatments survival was substantially higher for people taking them than is the case for untreated type 1 patients. When side-effects were reported for either drug, they were generally not serious. The EAG did not find any evidence about people with type 0 or type 4 SMA, which people in the qualitative analysis suggested may lead to an equality issue.

The EAG also looked at data that has been collected for various outcomes during the MAA period for both nusinersen and risdiplam. The results from the MAA suggest that both nusinersen and risdiplam separately could maintain or improve motor function across all SMA types. There was generally more data for nusinersen compared to risdiplam. This is because the MAA for risdiplam started after the one for nusinersen. For outcomes that were reported by patients, which generally assessed quality of life, there was a lack of data for both nusinersen and risdiplam. What data was available suggested that people maintained or improved their score for some measurements but for others there were mixed results. Importantly, the number of people who died was small and these deaths were not linked to either of the treatments.

When the EAG looked at published evidence about the economic impacts of the treatments, it was found that there was a lack of real-world evidence and the studies were all very varied in how they analysed the data. This meant that a lot of assumptions were made around the costs, survival rates, disease progression, and treatment effects.

Finally, the EAG looked at how cost-effective nusinersen and risdiplam are for treating people with presymptomatic, type 1, and type 2/3 SMA. By "cost-effective", we mean that the price per quality-adjusted life year (a measure of the burden of a condition that includes both the quality and the quantity of life lived) is below the threshold NICE would be willing to pay. The results from the analysis indicated that nusinersen

[REDACTED]

For risdiplam, the results from the EAG's analysis indicated that it was

[REDACTED]



What the EAG's results mean

What the EAG found in their report is aligned with what has been reported by the companies who make the treatments, and by other international health agencies. However, because there is limited evidence about nusinersen and risdiplam, the results should be viewed cautiously. Without strong data, it is difficult to confidently say which treatments provide the most benefit. Therefore, more research about nusinersen and risdiplam is needed. This should include research surrounding outcome measures that patient groups and professionals highlighted as being important to the community, such as bulbar function, stamina and fatigue, activities of daily living, the impact on carers and families, and independence.

Abbreviations

6MWT	6 minute walk test
ADL	Activities of Daily Living
AE	Adverse events
AIC	Akaike's Information Criterion
ATEND	Adapted Test of Neuromuscular Disorders
BiPAP	Bilevel positive airway pressure
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
BI	Budget impact
BIC	Bayesian information criterion
BSC	Best supportive care
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CGIC	Clinical global impression of change
CGI-S	Clinical global impressions - severity
CHMP	Committee for Medicinal Products for Human Use
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	Confidence interval
CrI	Credible interval
CLIP-Q	Conducting collaborative and intensive pragmatic qualitative research
CPAP	Continuous positive airway pressure
CS	Company's submission
CSR	Clinical study report
DMD	Duchenne muscular dystrophy
DMT	Disease-modifying therapy
DSU	Decision Support Unit
EAG	Evidence Assessment Group
EAP	Expanded Access Programme
EK2	Egen Klassifikation 2
ESS	Effective sample size
FAD	Final appraisal document
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HFMSE	Hammersmith Functional Motor Scale (expanded)
HINE-2	Hammersmith Infant Neurological Examination - Part 2
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
HST	Highly Specialised Technology
HTA	Health technology assessment
IC	Indirect comparison
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
ITC	Indirect treatment comparison
ITT	Intention-to-treat
LY	Life year
MAIC	Matching-adjusted indirect comparison
MeSH	Medical subject headings
MFM32	Motor Function Measure
MEP	Maximal expiratory pressure
MIP	Maximal inspiratory pressure

MMRM	Mixed model repeated measures
MTA	Multiple Technology Appraisal
MTC	Mixed treatment comparison
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NIV	Non-invasive ventilation
NMA	Network meta-analysis
NR	Not reported
OA	Onasemnogene abeparvovec
OS	Overall survival
PAS	Patient access scheme
PCF	Peak cough flow
PFS	Progression-free survival
PFVC	Predicted forced vital capacity
PGI-I	Patient global impression of improvement score
PGI-S	Patient global impression of severity score
PROMIS	Patient-reported outcomes measurement information system
PROMS	Patient-reported outcome measures
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RHS	Revised Hammersmith Scale
RR	Risk ratio
RP	Respiratory plethysmography
RULM	Revised Upper Limb Module
SAE	Serious adverse events
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMN	Survival of motor neuron protein
SNIP	Sniff nasal inspiratory pressure
SoC	Standard of care
SMA	Spinal muscular atrophy
SMAIS-ULM	SMA Independence Scale – Upper Limb Module
STA	Single Technology Appraisal
STC	Simulated treatment comparison
TA	Technology Assessment
TEAE	Treatment emergent adverse events
TTO	Time trade-off
TSD	Technical support document
TTOT	Time-to-off treatment
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
WTP	Willingness-to-pay

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4 Background

4.1 Introduction

This report describes the latest stage in the Multiple Technology Assessment (MTA) investigating the clinical and cost effectiveness of nusinersen and risdiplam for Spinal Muscular Atrophy (SMA). Nusinersen and risdiplam were reviewed separately in TA588 and TA755 respectively in 2019 and 2021, and both were recommended under a managed access agreement (MAA) with the instruction to collect further longer term data.^{2,3} Following the MAA periods, an MTA was initiated in 2023 which comprised critical appraisal of the companies' submitted evidence, systematic reviews of the clinical and cost effectiveness evidence, and an independent economic evaluation.¹ This report by the Newcastle External Assessment Group (EAG) describes an update to the systematic literature reviews of clinical and cost effectiveness, further critique of the company submissions, and a separate independent economic evaluation. It also includes analysis of the data (both quantitative and qualitative) from the MAA and a qualitative analysis of data submitted from patient groups which provide important context to the data from other sources.

4.2 Description of SMA

SMA is a rare, progressive neuromuscular disease most commonly caused by a genetic mutation in the survival motor neuron (SMN1) gene situated on chromosome 5q. Healthy people have both the SMN1 gene, which produces the functional full-length SMN protein, and the SMN2 gene, which produces mostly degraded and only a small amount of functional SMN protein. People with SMA have a faulty SMN1 gene and a varying number of SMN2 gene copies so their ability to produce SMN protein is reduced. This causes the gradual breakdown of motor neurons in the spinal cord and brainstem, leading to progressive muscle weakness, atrophy and eventually paralysis in late-stage disease. It affects muscles that involve crawling, walking, arm movement, head and neck movement, swallowing and breathing.^{4,5,6}

SMA is diagnosed through genetic testing and clinical examinations. It has historically been categorised into types 0, 1, 2, 3, and 4 according to age of onset (see Table 1), and the onset of neuromuscular weakness can range from birth to adulthood. Presymptomatic SMA is defined as SMA detected through genetic testing before the appearance of clinical symptoms. Although this classification system does not always accurately capture the patient experience, and is being impacted by the change in prognosis resulting from the availability of treatments, it has been used in the marketing authorisation and some of the clinical evidence and continues to be used in this report.

Table 1: SMA types (taken from Mercuri's SMA primer)⁴

SMA type	Typical age at presentation (range)	Maximal motor function achieved with supportive care	Feeding and communication	Pulmonary function	Survival^a with supportive care
0	Foetal	Nil	Nil	Very poor	Days–weeks
1	3 months (0–6 months)	No sitting or rolling	Poor, requires support	Poor, requires support	Months (median ~10 months)
2	12 months (7–18 months)	Sits, no walking	Variably affected	Reduced, often needs support	Years (median >20 years)
3	3 years (1.5–10 years)	Walks (limited)	Normal	No symptoms, mild reduction possible	Normal
4	>18 years	Walks (normal)	Normal	Normal	Normal
^a Survival is according to natural history and includes 'event-free survival' (ventilation support for <16 h/day for ≥14 days) Abbreviations: SMA = spinal muscular atrophy					

Type 1 SMA is the most common type of disease, occurring in 60% of cases. It is often referred to as early-onset or infantile-onset SMA as it manifests during the first six months of life. It involves rapid degeneration of motor neurons and subsequent reduction in motor function within months. Early treatment leads to better prognosis, but treatment initiation can lead to significantly improved motor function up to and beyond one year of age.

Types 2 and 3 SMA are often referred to as later-onset SMA, as they manifest between six and 18 months, and above 18 months to 18 years respectively. Progression does not tend to be linear and different children will improve, stabilise and deteriorate at different times, so it is difficult to predict the response to treatment. It should be noted that there can be overlap in functional status between type 1 patients and type 2/3 patients in terms of whether they are able to sit supported or stand.

Type 4 SMA presents in adulthood (adult-onset) and although it is milder than other types and does not affect lifespan, it leads to muscle weakness.

Type 0 SMA, also known as congenital SMA, is already evident in utero and babies tend to be born with severe weakness and respiratory distress, with a lifespan of days or weeks.⁷

Presymptomatic SMA is defined as genetically confirmed 5q SMA but lacking any clinical signs or symptoms. It can be identified by newborn screening and is usually identified in the UK through genetic testing prompted by a family member with the disease. Trials have demonstrated that a significant proportion of treated presymptomatic patients achieve motor milestones at a similar time to their healthy peers.⁵

One of the prognostic factors for SMA is the number of copies of a gene called SMN2. SMN2 can partially compensate for deficiencies in SMN1; on average a lower number of copies of

SMN2 correlates with poorer prognosis although this is not the case for all individuals. Most patients with type 1 SMA have two SMN2 copies, most with type 2 have three SMN2 copies and patients with type 3 tend to have either three or four SMN2 copies.⁴

Other prognostic factors include the amount of time that passes and the severity of functional impairment before treatment initiation; more time and more severe impairment tends to lead to a poorer prognosis and poorer response to treatment. The EAG learned from a clinical expert that the amount of physiotherapist input can influence the development of contractures which restricts function. Differences in physiotherapist input can arise from the level of core health services in different geographical areas, the availability of regular physiotherapy during the school day, and the amount by which families have the resources to top this up.

SMA has a substantial effect on the quality of life of patients, caregivers and their families.^{8,9} People with SMA experience considerable impairment in mobility, dexterity, pain and emotional wellbeing.⁸ They often experience challenges with independence, which can lead to feelings of isolation and hinder initiation or maintenance of close relationships and opportunities to socialise.⁹ Limitations in mobility influence accessibility to school, work and social activities.¹⁰ Fatigue affects people of all ages and types of SMA, affecting the ability to perform daily activities and participate in daily life.^{10,11} Individuals with SMA often require continuous support, which may involve full-time care and attention. This support demands significant physical effort, such as lifting and carrying, and can lead to sleep deprivation for both patients and caregivers. Additionally, it can cause stress and anxiety related to the potential loss of abilities in the future. The impact on mental health including anxiety, depression and social isolation can be severe for both adolescents and adults with SMA and their carers.^{10,11} Complications of SMA such as scoliosis (curvature of the spine) can add to a person's difficulties with movement and cause pain due to the compression of internal organs.

4.3 Care pathway and guidelines

SMA is managed through multidisciplinary support care, which aims to minimise the impact of disability by addressing complications and improving quality of life. The care pathway has been developed for both paediatrics¹² and adult¹³ patients. The guidance was informed by the international standard of care.^{14,15} The treatment expectations are noted to be subjective and based on the individual patient needs. It is imperative to make sure the right treatment is provided to individuals; therefore the following must be considered: treatment access, access to supportive care, education level, geography, social isolation, information, peer-to-peer exchange and access to technology.^{12,13}

In paediatrics, babies showing the following signs may be suspected of SMA:¹²

- Floppiness
- Reduced movements in early weeks
- Recurrent chest infections
- Difficulty feeding
- Failure to gain weight
- Motor delay or loss/regression of skills
- Acute respiratory distress
- Acute respiratory distress requiring respiratory support

The child may be forwarded to a neuromuscular service within 1-14 days, depending on severity. Diagnosis is completed via an SMN1 genetic test (using a method called multiplex

ligation-dependent probe amplification). If confirmed, a multidisciplinary team should be deployed to meet the child's needs. This usually entails a co-ordinator who is responsible for all aspects of care, including:¹⁴

- Pulmonary care
- Acute care
- Other organ involvement
- Medication
- Nutritional, gastrointestinal and bone health
- Orthopaedic care
- Neuromuscular/rehabilitation

The condition should be continually managed using such specialist management, as above, and assess eligibility for treatment. Both nusinersen and risdiplam are currently provided by the MAA; onasemnogene abeparvovec (OA) is a gene therapy, see Table 2 for eligibility criteria of treatments. Treatment is agreed by the national multidisciplinary team.¹⁶ If treatment is not indicated, palliative care is undertaken.

Those with an established diagnosis will transition from paediatric care to adult care. Such transitions for those with chronic disabilities, such as SMA, is often difficult. Where adults are suspected as having SMA a referral can be made for diagnosis at this stage.¹³ Assessments for treatment and/or ongoing management occur within 18 weeks. Specialist management is carried out with a similar approach as for paediatrics, i.e. a multidisciplinary team. Currently, the MAA is the only way for treatments be accessed, if eligible, for the adult patients. Regular assessments should be made and reviewed. Non-sitters, sitters, and walkers likely have different orthopaedic and spine, motor, and nutrition, gastrointestinal and bone health requirements. For example, for non-sitters and sitters the orthopaedic and spine care should look to reduce impact on tight joints, prevent scoliosis, provide customised upright seating/standing frames, among other things. For patients who are ambulant, function and mobility, exercise (e.g. swimming), and stretching (for contractures) should be promoted, among other things.¹³

Table 2: Eligibility criteria for each available treatment: nusinersen, risdiplam and onasemnogene abeparvovec

Nusinersen eligibility criteria (MAA) ^{17,18}	Risdiplam eligibility criteria (MAA) ¹⁹	Onasemnogene abeparvovec eligibility criteria ¹⁶
People with early- (type 1) or later-onset (types 2 and 3) SMA People with presymptomatic SMA with homozygous gene deletion or homozygous mutation or compound heterozygous mutation of the SMN1 gene (chromosome 5) found via presymptomatic genetic testing No type 0 or type 4	Clinically confirmed type 1, 2 or 3 or with presymptomatic SMA and one to four SMN2 copies	Only if presymptomatic 5q SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene in babies aged 12 months and under If presymptomatic SMA develops into type 1 SMA, OA is an available treatment option in certain situations
No permanent ventilation (≥16 hours/day for 21 consecutive days in the absence of acute reversible infection) or tracheostomy requirement at baseline	No permanent ventilation (≥16 hours/day for 21 consecutive days in the absence of acute reversible infection)/ tracheostomy requirement at baseline. Patients who do not meet this criterion but otherwise meet the eligibility criteria should be discussed with the NHS England Clinical Panel	
Nusinersen is used as a monotherapy	Risdiplam is used as a monotherapy	
Must not have had successful treatment with onasemnogene abeparvovec	Must not have had successful treatment with onasemnogene abeparvovec^a	
Intrathecal injection must be technically feasible in the opinion of the treating clinician and not contraindicated	Mandated data items have been collected prior to starting treatment within this MAA. Patients who have started treatment for SMA prior to this MAA are not required to repeat an assessment if a previous assessment has captured all mandated data items within the last 6 months^b	

Must not have received spinal fusion surgery following a diagnosis of scoliosis which, in the opinion of the treating clinician, prohibits safe administration	Patient/carer has signed the 'Managed Access Patient Agreement' and agreed to the associated monitoring, clinical assessments and sharing of data for the purpose of the MAA	
Must not have severe contractures that, in the opinion of the treating clinician, prohibit measurement of motor milestones	Clinician confirms they will submit data to SMA reach; have made patient/carer aware that there are other treatments for SMA, which may be more suitable for that patient; and confirm annually, via Blueteq form, that the patient continues to receive benefit from treatment	
Patient scope: Clinical diagnosis of SMA type 1, 2, or 3; presymptomatic SMA confirmed to have SMA via genetic testing and has one to four SMN2 copies ^a Successful treatment with OA defined as a reduction in motor ability: total worsening of scale score corroborated by two consecutive measurements from any two scales (>2 points on horizontal kick or 1 point on other HINE scores [excluding voluntary grasp], >4 points on CHOP-INTEND, or >3 point on RHS); AND/OR a deterioration in respiratory function: an increasing requirement for respiratory support overnight and/or, for that patient, an uncharacteristic increase in respiratory infections requiring hospital treatment that cannot be accounted for by aspiration or intrinsic lung disease ^b Mandatory data items listed in table 2 (section 7) of risdiplam MAA¹⁹		

4.4 Measurement of disease outcomes

Various challenges exist in measuring response to treatment in people with SMA. Because the disease affects people from newborns into adulthood, different scales are used to measure motor function accounting for comparative 'normal' development history. When different scales are used in trials it makes it difficult to be sure that the results are comparable and measuring the same thing. The EAG was informed by a clinical expert that when children get to the point that they need to switch scales, it can be concerning for patients and carers that they see a change from a high score on the previously used scale to a low score on the new scale, so they use both initially for reassurance. SMA also affects people with very different levels of severity ranging from permanent ventilation, a feeding tube and very little voluntary movement, through to a relatively small amount of muscle weakness. Access to 'best supportive care' is variable and inequitable in the UK. Patients and carers have reported that commonly used outcome measures do not successfully reflect their lived experience, and can have a negative impact if they receive a low score despite feeling improvement and satisfaction in their lives.¹¹ It can also be the case that a 'small' change in terms of outcome measure can reflect a huge impact in terms of daily life for both patient and carer, such as the ability to operate one's own wheelchair. Because fatigue is such a common symptom of SMA, the time of day at which measurements are made can influence the scores – the same person may score lower later in the day when they are feeling more fatigued. All of this makes defining a clinically significant response to treatment challenging.

4.4.1 Motor function

Because SMA has such a variety of severity and can begin from very early life through to adulthood, different outcome measures are used to measure motor function as appropriate to age and severity (see Table 3). It should be noted that, particularly for children, outcome scores can vary for reasons other than motor function decline; for example if there is spinal fusion or spinal surgery their scores will dip before returning, and if they experience a growth spurt their motor function may appear to decline as their muscles are dealing with more weight. It is important to capture both age-appropriate gross motor milestones and fine motor skills. This can all make it difficult to compare across studies. Patients have reported that motor outcome measures do not always capture important improvements – for example, even very small improvements in fine motor skills and upper limb function were identified as very important because they allow patients to maintain independence.³

Table 3: Outcome measures for motor function

Outcome measure	Outcome measure name in full (where appropriate)	Description
WHO Motor Development Milestones		Tracks gross motor development milestones in infants and young children.
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders	Assesses motor skills (such as spontaneous movement of upper and lower extremity, hand grasping, rolling, and head control) in infants with SMA. Change of ≥ 4 in CHOP-INTEND represents an estimate of a meaningful improvement in motor function. CHOP-INTEND was described to the EAG by a clinical expert as the most useful outcome measure for infants.
HINE-2	Hammersmith Infant Neurological Examination - Part 2	Evaluates motor milestones (head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking) in infants and young children with SMA. Achievement of important motor milestones and higher scores on the HINE-2 scale (≥ 2 -point increase in the ability to kick [or maximal score] or a 1-point increase in head control, rolling, sitting, crawling, standing, or walking) are therefore considered to be a clinically relevant improvement for an infant with type 1 SMA.
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition	Assesses developmental functioning in infants and toddlers, including motor skills such as head control, sitting, crawling, kicking. The ability to achieve a sitting position unsupported at 12 months, as measured by the BSID-III, is considered a clinically meaningful and important milestone in type 1 SMA.
RHS	Revised Hammersmith Scale	Evaluate a broad spectrum of motor functions in SMA (including 10m run test, 6m walk test, rise from floor for ambulant type 2/3 SMA patients).
HFMS/E	Hammersmith Functional Motor Scale (expanded)	Assesses motor function (sitting, rolling, transitions relating to crawling and kneeling, and standing/stepping, but no items to assess the fine motor function of the hand, wrist, or elbow) in non-ambulant individuals with type 2 or 3 SMA. A change of ≥ 0 in HFMS total score representing stabilisation or improvement of

Outcome measure	Outcome measure name in full (where appropriate)	Description
		motor function is clinically meaningful and a change of ≥ 3 in HFMSE represents an estimate of a meaningful improvement in motor function.
RULM	Revised Upper Limb Module	Assessment of upper limb motor performance, including shoulder, elbow, wrist and hand function, in people with SMA. A change of ≥ 0 in RULM total score representing stabilisation or improvement of motor function is clinically meaningful, and a change of ≥ 2 represents an estimate of a meaningful improvement in motor function.
MFM32	Motor Function Measure	Assesses motor function abilities in individuals with neuromuscular diseases, including SMA. It assesses three domains of motor function: D1 (standing and transfers), D2 (axial and proximal motor function), and D3 (distal motor function).
ATEND	Adapted Test of Neuromuscular Disorders	Clinical rated outcome in development for children and adults with SMA who are no longer able to sit or who have never been able to sit. A change of ≥ 0 in MFM32 total score representing stabilisation or improvement of motor is clinically meaningful in this patient population, and threshold of improvement on the MFM32 scale, such as ≥ 3 points, should be considered as a marked improvement for patients as it may represent either the acquisition of a new function or the improvement in performance of several functions.
CMAP	Compound Muscle Action Potential amplitude	Measures the electrical response of muscles to nerve stimulation, indicating motor neuron health.
MUNIX	Motor unit index	A biomarker used to assess loss of motor units in later-onset SMA patients.
ALSFRS-R	Revised Amyotrophic Lateral Sclerosis Functional Rating Scale	Considers bulbar, fine and gross motor (upper and lower limbs), and respiratory outcomes original used for those with amyotrophic lateral sclerosis but is used in SMA assessment (validation is lacking).

Outcome measure	Outcome measure name in full (where appropriate)	Description
MRC-SS	Medical Research Council Sum Score	Assessment of muscular strength.
MMT	Motor Muscle Testing	Assessment of muscular strength.
MUNE	Motor Unit Number Estimation	An electrophysiological method of estimating the number of motor neurons innervating a muscle group.
GFFS	Grip and Finger Flexion Strength	Measurement of grip strength.
6MWT	6-Minute Walk Test	Sub-maximal functional exercise test to assess aerobic capacity and endurance, maximum distance covered in 6 minutes.
TUG	Timed Up and Go	Timed test where patients are required to stand up from a chair, walk to a line at normal pace (3 metres away), walk back to the chair and sit down again.

4.4.2 Bulbar function

Bulbar function impacts a person's ability to swallow and communicate verbally. This can be measured by nutritional support (including nasogastric feeding and gastrostomy), swallowing function, and speech therapy support.

4.4.3 Frequency and duration of hospitalisation

The most frequent reason for hospitalisation is respiratory events. Hospitalisations are measured in terms of admission rates, number of admissions, proportion of time hospitalised, patient years, or days in hospital. Sometimes they are reported as AEs.

4.4.4 Respiratory function

Because SMA influences the respiratory muscles, it is important to measure respiratory function. Several outcome measures are used (Table 4).

Table 4: Outcome measures for respiratory function

Outcome measure	Outcome measure name in full (where appropriate)	Description
FEV1	Forced expiratory volume in one second	Measures the amount of air a person can forcibly exhale from the lungs in the first second of a forced breath.
FVC	Forced vital capacity	Measures the total amount of air a person can forcibly exhale from the lungs.
MEP	Maximal expiratory pressure	Assesses the strength of expiratory muscles.
MIP	Maximal inspiratory pressure	Assesses the strength of inspiratory muscles.
NIV	Non-invasive ventilation usage	Tracks the use of ventilatory support in individuals with SMA.
PCF	Peak cough flow	Assesses the strength of cough, indicating respiratory muscle function.
PEFR	Peak expiratory flow rate	Measures how fast a person can exhale air from their lungs.
PFVC	Predicted forced vital capacity	Estimates the expected FVC based on demographic factors.
RP	Respiratory plethysmography	Measures thoraco-abdominal movements to assess respiratory patterns.
SNIP	Sniff nasal inspiratory pressure	Measures inspiratory muscle strength via nasal pressure.

Tracheostomy		A surgical procedure to create an opening in the neck to place a tube into a person's windpipe, aiding in breathing.
VC	Vital capacity	Maximum amount of air a person can exhale after taking the deepest breath possible.

4.4.5 Complications

The most common complications of SMA are scoliosis or curvature of the spine, and muscle contractures which reduce the person's range of motion, both of which cause pain. Other complications include the need for support with feeding and the risk of aspiration pneumonia.

4.4.6 Non-invasive or invasive ventilation

People with type 1 SMA may require non-invasive ventilation or cough-assist as much as daily. Non-invasive ventilation methods include Bilevel Positive Airway Pressure (BiPAP) or Continuous Positive Airway Pressure (CPAP), whilst invasive ventilation uses an endotracheal tube (through the mouth) or tracheostomy (inserted through the neck). Permanent ventilation is defined as tracheostomy or ≥ 16 hours ventilation per day continuously for at least 21 consecutive days. The EAG learned from a clinical expert that although it is unusual for a person not to remain on permanent ventilation once they get there, it does not necessarily preclude a participative and relatively good quality of life.

4.4.7 Stamina and fatigue

SMA very commonly affects stamina and fatigue levels, which have an important impact on day-to-day life.

4.4.8 Mortality

According to natural history studies, the mean age at death of patients with type 1 SMA is 19.2 months (SD 10.1 months).²⁰ Patients with type 2 SMA would be expected to survive into adulthood and those with type 3 tend to have a normal lifespan. Therefore, the impact on mortality for type 1 patients is key.

4.4.9 Adverse effects of treatment

The most common adverse effects associated with nusinersen are headache, back pain and vomiting, which are usually associated with administration via lumbar puncture rather than the drug itself. Other potential adverse effects of nusinersen include renal toxicity, thrombocytopenia and coagulation abnormalities, and hydrocephalus.

The most common adverse effects associated with risdiplam are fever, rash, diarrhoea, and headache.

4.4.10 Health-related quality of life and PROMs

Table 5: Outcome measures for health-related quality of life

Outcome measure	Outcome measure name in full (where appropriate)	Description
ACEND	Assessment of Caregiver Experience with Neuromuscular Disease	Quantifies caregiver impact experienced by parents of children affected with severe neuromuscular diseases, including children with SMA
Caregiver Burden Scale		Assesses the impact of caregiving on the caregiver's quality of life.
EQ-5D-5L	EQ-5D-5L (5 level version)	Self-report survey that measures quality of life across 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression
EQ-5D-Y	EQ-5D-Y (youth version)	Child-friendly version of EQ-5D-5L allowing patient reporting by young people from eight years of age
INQoL	Individualised Neuromuscular Quality of Life Questionnaire	Individualised neuromuscular quality of life tool; a patient-reported tool specific to patients with neuromuscular diseases
ITQoL-SF47	Infant Toddler Quality of Life Questionnaire 47-item Short-Form	Infant toddler quality of life questionnaire; for children between two months and five years of age.
PedsQL	Pediatric Quality of Life Inventory	Paediatric quality of life inventory; a brief measure of patient reported health-related quality of life in children and young people
QoL-NMD	Quality of Life in Neuromuscular Disease Questionnaire	Quality of life in neuromuscular disease; a patient reported outcome measure designed for patients with a slowly progressive neuromuscular disease with motor deficiency
SF-36	36-item Short-Form Survey	Short-form health survey; a patient-reported measure of general health status
PGI-S	Patient Global Impression of Severity	A single question asking the patient to rate how their condition is now on a scale

Outcome measure	Outcome measure name in full (where appropriate)	Description
PGI-I	Patient Global Impression of Improvement	A single question asking the patient to rate their perception of improvement on a scale
EK-2	Egen Klassifikation 2	Aims to focus on meaningful changes that benefit from intervention, including eating, chewing, use of hands and fatigue
SMAIS-ULM	SMA Independence Scale-Upper Limb Module	To assess the degree of assistance required to perform typical daily activities in individuals with Type 2 and 3 (non-ambulatory) SMA
CGI-I	Clinical Global Impression Improvement	A single question asking the clinician to assess improvement or worsening of a patient's condition

4.5 Description of technologies under assessment

Because nusinersen and risdiplam have very different administration routes and schedules, they give patients a choice between a daily oral dose at home (convenient but constant) or a quarterly spinal injection in hospital (less convenient but patients can forget about treatment between injections). Patients may choose to switch from nusinersen to risdiplam, for example if scoliosis starts to influence the success of injections, or from risdiplam to nusinersen, for example if they are considering starting a family.

4.5.1 Nusinersen

Nusinersen (Spinraza, Biogen) is a 2'-O-methoxyethyl antisense oligonucleotide which stimulates the survival motor neuron SMN2 gene to increase SMN protein levels.⁶ It is administered by intrathecal injection, and where patients are very young or have difficult spines (e.g. deformities or fusions) doctors can use ultrasound or other imaging techniques to aid administration. The intrathecal injection (12mg/5mL) requires an initial loading phase of four doses, the first three doses are taken at 14-day intervals and the fourth dose 30 days after the third dose. Maintenance doses are then provided every four months.

Nusinersen was originally assessed under TA588, which showed the treatment improved a range of outcomes that are important to people with type 1, 2 and 3. However, there was a lack of long-term evidence, leading to uncertainty of the efficacy of the treatment. The committee recommended further data collection would help address such uncertainty. Additionally, the cost-effectiveness estimates presented were higher than what NICE usually considers to be a cost-effective use of NHS resources. Again, interpretation of the potential cost implications was difficult due to limited long term evidence. Additionally, it was unable to distinguish between the SMA subtypes and what differences could be achieved in various SMA patients. The committee therefore recommended the treatment was made available through an MAA for patients with 5q SMA if they have presymptomatic, type 1, 2 or 3 disease. No evidence was presented by the company for types 0 or 4.

For type 1, 2, and 3 SMA, the committee noted that nusinersen improves motor function but other health benefits were less certain. Survival outcomes were improved for type 1 but other health outcomes were uncertain. Little data was available for the presymptomatic population. Due to this uncertainty the managed access agreement provided for further data to be collected. The committee noted that there may be a delayed response to nusinersen for some people (for at least 2 years).

4.5.2 Risdiplam

Risdiplam (Evrysdi, Roche) is a small-molecule survival motor neuron-2 (SMN2) gene splicing modifier which increases SMN protein levels in the central nervous system. It is administered orally through an oral syringe once per day.

Risdiplam was originally assessed under TA755, which showed the treatment improved motor function in SMA type 1, 2 and 3. Additionally, there was evidence that those with type 1 may live longer when being treated with risdiplam. Some evidence also suggested risdiplam may be effective for people with presymptomatic SMA. However, there was a lack of evidence comparing risdiplam with usual care in type 1 patients. Furthermore, there was a lack of long-term evidence, making judgements uncertain. The cost-effectiveness estimates were higher than what NICE usually considers to be a cost-effective use of NHS resources. The committee therefore recommended the treat was made available through an MAA for patients with 5q SMA if they have type 1, 2, or 3 disease, or presymptomatic SMA with 1 to 4 SMN2 copies.

The committee concluded that risdiplam improves motor function in SMA types 1 to 3, and interim trial data showed some evidence of improvement in motor function for presymptomatic SMA. There was some evidence that risdiplam improves survival in people with type 1 SMA.

The committee decided that the evidence would be reviewed when the final results of the key trials in SMA type 1 and type 2/3 (FIREFISH and SUNFISH) are published, and this report incorporates these results.

4.5.3 Identification of important subgroups

The important subgroups are defined in the NICE decision problem, which can be seen in Section 5.

4.6 Layout of report

This report provides the EAG critique of each company's submission. It then describes the methods of each element of the EAG's work, beginning with the qualitative analysis of submissions and meeting content, then the update of the previous clinical effectiveness SLR, the update of the cost-effectiveness SLR, and finally the EAG's cost-effectiveness analysis. The results of the clinical effectiveness and cost-effectiveness SLRs are presented, followed by the EAG's cost-effectiveness analysis. The MAA data is provided for outcomes where appropriate. Qualitative results are presented in a separate section after the quantitative results. Finally, we present the EAG's conclusions.

5 Definition of the decision problem

The final scope as defined by NICE is reproduced in Table 6.

Table 6: NICE decision problem

Domain	Eligibility
Interventions	- Nusinersen - Risdiplam Interventions are monotherapies in addition to existing clinical services and established clinical management.
Population	People with types 0, 1, 2, 3 or 4 5q SMA, or presymptomatic 5q SMA confirmed with genetic testing, with 1 to 4 SMN2 copies
Subgroups	If the evidence allows the following subgroups will be considered: - Number of SMN2 gene copies in people with presymptomatic SMA - Functional status (non-sitter, sitter, walker) - People who have had prior active treatment for SMA
Comparators	- Established clinical management - Best supportive care The interventions will be compared to each other In addition, for children aged 12 months and under with a biallelic mutation in the SMN1 gene and present with a clinical diagnosis of type 1 5q SMA or presymptotically with up to 3 copies of the SMN2 gene - Onasemnogene abeparvovec
Outcomes	The outcome measures to be considered include: - motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills) - bulbar function (including, for example, swallowing and ability to communicate) - frequency and duration of hospitalisation - respiratory function - complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) - need for non-invasive or invasive ventilation - stamina and fatigue - mortality - adverse effects of treatment - health-related quality of life (for patients and carers)
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.

	The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.
Abbreviations: SMA = spinal muscular atrophy; SMN2 = survival motor neuron 2	

After considering the consultation responses and meeting with patient and professional groups, the EAG added further outcomes to consider (in consultation with NICE), where data were available:

- Ability to socialise
- Activities of daily living
- Psychological impact
- Independence
- Impact on education
- Impact on family and carers
- Impact on the ability to work
- Looking to the future
- Maintenance or stabilisation of condition
- Patient choice
- Spectrum of SMA

6 Critique of Biogen submission

6.1 Biogen decision problem

The Biogen decision problem is reproduced in Table 7, followed by a critique of the submitted systematic review.

Table 7: Biogen decision problem, reproduced from Biogen document B, table 1

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with types 0, 1, 2, 3, or 4 5q SMA, or presymptomatic 5q SMA confirmed with genetic testing with 1 to 4 <i>SMN2</i> copies	Presymptomatic SMA and SMA types 1, 2 and 3	The evidence base on nusinersen is limited to people with presymptomatic SMA, and symptomatic infantile-onset (type 1) and later-onset SMA (types 2 and 3). Type 0 SMA was excluded from the submission due to futility of treatment for these patients. The evidence base on nusinersen in type 4 SMA is insufficient for HTA purposes, hence this population is also excluded from cost-effectiveness modelling.
Intervention	- Nusinersen - Risdiplam Interventions are monotherapies in addition to existing clinical services and established clinical management.	Nusinersen	Not applicable; Biogen are the manufacturer of nusinersen only.
Comparator(s)	- Established clinical management - Best supportive care - The interventions will be compared to each other In addition, onasemnogene abeparvovec will be considered as a comparator for	Direct evidence is presented comparing nusinersen with established clinical management/best supportive care. Indirect evidence only is available against risdiplam and	The sham control used in phase III ENDEAR and CHERISH trials can be considered to represent established clinical management/ best supportive care. No direct evidence is currently available against risdiplam or

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	children aged ≤ 12 months with a biallelic mutation in the <i>SMN1</i> gene and present with a clinical diagnosis of type 1 5q SMA or presymptotically with up to 3 copies of the <i>SMN2</i> gene	onasemnogene abeparvovec. This is subject to substantial uncertainty due to differences in trial populations and outcome assessments.	onasemnogene abeparvovec; consequently, ITCs were performed with the aim to inform relative efficacy. However, limitations of the ITCs render them unsuitable to inform cost-effectiveness modelling. Therefore, this submission focuses on the comparison between nusinersen and BSC.
Outcomes	• Motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills) • Bulbar function (including, for example, swallowing and ability to communicate) • Frequency and duration of hospitalization • Respiratory function • Complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation • Stamina and fatigue • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers)	As specified in the NICE scope.	Maintenance of respiratory function, which is most critical in type 1 SMA was included in the primary endpoint of the ENDEAR trial, i.e., time to death or permanent ventilation, with long-term assessment continued in the SHINE open-label extension. Information on stamina and fatigue, as measured using the 6-Minute Walk Test, is limited to ambulant patients.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Economic analysis	- The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. - The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. - Costs will be considered from an NHS and Personal Social Services perspective. - The availability of any commercial arrangements for the intervention, comparator, and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.	As per the reference case	Not applicable
Subgroups to be considered	If the evidence allows the following subgroups will be considered: - Number of <i>SMN2</i> gene copies in people with presymptomatic SMA - Functional status (non-sitter, sitter, walker) - People who have had prior active treatment for SMA	- Subgroup analyses stratified by <i>SMN2</i> copy number are available for the presymptomatic population treated in NURTURE - Subgroup analyses stratified by functional status and prior therapy are available from the	Subgroup analyses stratified by functional status and prior therapy are at present only available from the real-world data collection as part of the Managed Access Agreement established by TA588; no data is stratified by functional status from the clinical development programme. The

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		Managed Access Agreement established by TA588	efficacy of nusinersen in patients who received prior therapy is currently being assessed in the ongoing studies ASCEND and RESPOND, which include patients previously treated with risdiplam and onasemnogene abeparvovec.
Special considerations including issues related to equity or equality	None stated	Although nusinersen will be appraised through a multiple technology appraisal, its assessment is anticipated to have several features that are commonly seen in the highly specialised technologies programme. Therefore, decision modifiers and flexibility in NICE's decision making should be taken into account.	Not applicable
Abbreviations: BSC = best supportive care; ITC = indirect treatment comparison; NICE = National Institute for Health and Care Excellence; SMA = spinal muscular atrophy; SMN2 = Survival Motor Neuron 2; TA = Technology Appraisal			

6.2 Critique of Biogen SLR

6.2.1 Search strategies

The company conducted the original search in January 2023 and updated this search in November 2023. A range of electronic bibliographic databases were searched, and the company did not report the use of search filters. Conference abstracts were sought on multiple databases year by year, from 2020 to 2023 inclusive. The company state that date limitations of 2020 onwards, removal of animal studies and case reports were imposed on the searches.

The search strategy encompassed concepts from the SMA population, combined with the nusinersen, onasemnogene abeparvovec (OA) or risdiplam concepts of the decision problem.

The EAG appraised the searches using the PRESS checklist and the latest NICE methods manual.^{21,22} The number of records retrieved per search line was shown and the methods and terms used to search the conference abstracts were presented as might be expected when using the PRISMA-S reporting guidance.²³

6.2.2 Inclusion and exclusion criteria

6.2.2.1 Population

The Biogen SLR included patients with presymptomatic SMA and SMA types 0, 1, 2, 3, 4, and they planned to extract data about all these populations (Table 7). However, in the submission they stated that patients with type 0 or type 4 SMA were excluded. They cited clinical expert advice that treatment for type 0 patients is futile and that there was insufficient evidence to inform evaluation for type 4 patients.

6.2.2.2 Intervention

Interventions included nusinersen and risdiplam as monotherapies in addition to established clinical management.

6.2.2.3 Comparators

Comparators comprised established clinical management, BSC, or OA in patients eligible for that treatment. Biogen noted that direct evidence is only available comparing nusinersen and best supportive care. They conducted indirect comparisons (ITCs), which are discussed in Section 6.2.4.

6.2.2.4 Outcomes

Biogen included all the outcomes listed within the decision problem, as well as specifying outcomes relating to speech and communication, growth, and use or discontinuation of concomitant medications. They noted that pulmonary function is only available from real world evidence.

6.2.3 SLR methods

The EAG have few concerns about the eligibility criteria of the Biogen SLR and the methods of the review. The restriction to studies that included at least 100 participants meant that a number of eligible smaller studies were omitted, but no controlled studies. See Table 8 for explanation of the methods for each step of the SLR. The EAG's assessments (detailed in bold) are on a three-point Likert scale (key concern, some concerns or appropriate).

Table 8: EAG evaluation of Biogen SLR

Systematic review stage	Section in CS where methods are reported	EAG's assessment of the robustness of methods
Data sources	Appendix D section 2.1	Appropriate Multidisciplinary electronic databases were searched and described in full. Relevant conferences for SMA have been searched and justification has been given where access was limited or prevented. The company searched for ongoing/unpublished studies via trial registries.
Search strategies	Appendix D section 2.1	Appropriate Relevant search terms were used and combined appropriately. The searches did not use exclude by using Boolean "NOT" terms. No limitations have been applied without justification.
Search filters	Appendix D section 2.1	Appropriate Study design filters were not used, except the removal of news, editorials and case studies, which were reported and justified appropriately.
Eligibility criteria	Appendix D section 1	Some concerns Eligibility criteria matched the NICE decision problem in terms of population, intervention, comparators and outcomes. They included RCTs, non-randomised controlled trials, single-arm interventional trials (with or without a historical control group), prospective or retrospective comparative observational studies, and non-comparative observational studies that include at least 100 participants. The latter condition omitted a sizable number of smaller studies which may affect the comprehensiveness of the results.
Screening	Appendix D section 2.2	Appropriate Both title and abstract and full text screening were each conducted by two reviewers independently, with disagreements adjudicated by a third reviewer.
Data extraction	Appendix D section 2.3	Appropriate One reviewer conducted data extraction using a piloted data extraction sheet in Excel. A second reviewer checked the data points, with a third reviewer adjudicating disagreements.
Quality appraisal	Appendix D section 2.4	Appropriate One reviewer conducted critical appraisal using Cochrane and JBI tools for specific study designs, and a second reviewer checked with a third reviewer adjudicating disagreements.
Data synthesis	Appendix D sections 3 and 6	Appropriate Since no trials were found comparing nusinersen to risdiplam or OA, the company conducted a feasibility assessment for an indirect comparison between the drugs. They conducted a series of MAICs for type 1 SMA but did not include the data in the models. They judged that heterogeneity was too great to conduct a network meta-analysis for type 2/3 SMA. The EAG agrees with the company's judgement.
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; JBI = Joanna Briggs Institute; MAIC = matching-adjusted indirect comparison; NICE = National Institute for		

Systematic review stage	Section in CS where methods are reported	EAG's assessment of the robustness of methods
Health and Care Excellence; OA = onasemnogene abeparvovec; SLR = systematic literature review; SMA = spinal muscular atrophy; RCT = randomised controlled trial; ROBINS-I = Risk Of Bias In Non-randomised Studies - of Interventions		

6.2.4 Critique of Biogen ITC

Biogen utilised unanchored matching-adjusted indirect comparisons (MAICs) for the comparison of nusinersen to either OA or risdiplam. They stated that available data did not allow for an anchored MAIC to be conducted. In the unanchored MAICs, all available covariates were included, where possible. If it was not possible, due to poor overlap of covariates or MAIC implementation not providing satisfactory matching (reweighting) between individual patient data (IPD) and aggregate data, a LASSO regression technique was applied to reduce the number of covariates. However, if a MAIC was still deemed unfeasible, a simulated treatment comparison (STC) was implemented. Additionally, all analyses took place using complete cases only. The company highlighted that such ITCs are in line with NICE Technical Support Document (TSD) 18,²⁴ and went on to state that specific care must be taken regarding the possible biases of such analyses. Specifically, that the amount of bias (systematic error) in these estimates is unknown, is likely to be substantial, and could even exceed the magnitude of treatment effects which are being estimated.

Fourteen analyses were conducted by Biogen (seven comparing nusinersen to OA and seven to risdiplam). When comparing to OA, most analyses suggest [REDACTED]

[REDACTED] at age 14 months in presymptomatic or type 1 SMA. However, for type 1, 'stands and walks alone at 18 months of age' (BSD-III) assessment was not formally possible via the MAIC due to no events (i.e. no patients achieved this milestone in nusinersen study; CS3-A or CS3-B). There was a [REDACTED] in type 1 SMA patients. However, these results should be interpreted with caution as the MAICs effective sample sizes (ESS) were mostly <30 (n = 5), two of which were <10. The remaining two were <35. These small ESS suggest a potential for high variability between the populations being compared, meaning the estimate may be unstable, in line with NICE TSD 18.²⁴

When comparing nusinersen to risdiplam, the same issues of ESS were apparent. Five of the available analyses were <30, which compared HINE-2 in type 1 subgroups (e.g. sitting without support). All analyses suggest [REDACTED] in type 1 SMA patients. The same can be said for overall survival 12 months into the study, which showed [REDACTED]. It is worth noting for this analysis that CHOP-INTEND at baseline was much higher in the nusinersen group compared to the risdiplam group (27.2 vs 22.0), and there was also a higher proportion of individuals with baseline feeding issues (48% vs 15%). For the outcomes of HFMSE and RULM (compared between baseline and 12 months) there were [REDACTED] between the two drugs. However, these analyses were derived using STCs due to a MAIC being deemed unfeasible because of failing to match covariates. The company suggest this was due to a lack of overlap at age of screening and symptom onset, leading to the MAIC failing to match the covariates. The company states that these are crucial covariates and therefore decided not to run LASSO to reduce the covariates in the MAIC, rather opting for the STC. The EAG

agrees with this assessment, however, as the results are derived from an STC, there may be inherent biases. For example, when data is non-linear, which can commonly be the case in SMA where it is possible to show improvements, maintenance or deterioration over time, results can be open to bias.²⁵ Specifically, as the results are generated via a linear regression model using IPD from one trial (in this case, nusinersen) compared to aggregate data from the comparator trial (risdiplam) the non-linearity assumption may be violated. If there is non-linearity substituting the mean covariate values from the comparator trial into the regression can lead to biased estimates, due to issues between the relationship of the mean of the outcome and the mean of the covariates.²⁶ Therefore, it is important to consider the results with caution.

The EAG note that additional consideration was needed for time frames when comparing between the studies. For example, HINE-2 assessments, IPD and aggregate data did not align. They therefore implemented the rule that a subject was included in the IPD if they had a HINE-2 or WHO motor milestone assessment at ≤ 24 months into the study, and if there was more than one publication for a study, the company used the publication with the latest time point. However, this may have biased the estimate against nusinersen, so to mitigate this they implemented the additional rule that if the assessment fitting the above condition was < 21 months into the study for a given subject, that subject was dropped from the comparison.

Overall, clear attempts were made to make the analyses possible and plausible with the data available to the company for statistical assessments. Some concerns arise with the comparability of the different cohorts, where the ESS is low after matching. Additionally, for type 2/3 the analysis is based on STC. However, given the inherent differences between the populations, not running an anchored MAIC may make sense clinically. Table 9 provides an overview of the results from the Biogen company submission.

Table 9: Overview of the results from the Biogen company submission

Outcome	Population	Analysis Type	Comparator	Covariates	Sample size/ ESS	Conclusion
WHO MM stands with support before 18 months	Presymptomatic	Unanchored MAIC	OA (STR1VE-EU and STR1VE-US)	Sex, age at first dose, weight, SMN2 copy number, baseline CHOP-INTEND score	NURTURE: 25/8.78	[REDACTED]
WHO MM walks alone before 18 months	Presymptomatic	Unanchored MAIC	OA (STR1VE-EU and STR1VE-US)	Sex, age at first dose, weight, SMN2 copy number, baseline CHOP-INTEND score	NURTURE: 25/8.78	[REDACTED]
BSID-III sitting without support at 18 months	Type 1	Unanchored MAIC	OA (STR1VE-EU and STR1VE-US)	Sex, age at screening, age at symptom onset, weight, SMN2 copy number, baseline ventilation support (yes/no), baseline feeding issues (yes/no), baseline CHOP-INTEND score.	CS3A and CS3B: 46/12.61	[REDACTED]
BSID-III stands with support at 18 months	Type 1	Unanchored MAIC	OA (STR1VE-EU and STR1VE-US)	Sex, age at screening, age at symptom onset, weight, SMN2 copy number, baseline ventilation support (yes/no), baseline feeding issues (yes/no), baseline CHOP-INTEND score.	CS3A and CS3B:46/12.61	[REDACTED]
BSID-III walks alone at 18 months	Type 1	Unanchored MAIC	OA (STR1VE-EU and	Sex, age at screening, age at symptom onset, weight, SMN2 copy number, baseline ventilation support	CS3A and CS3B:46/12.61	[REDACTED]

Outcome	Population	Analysis Type	Comparator	Covariates	Sample size/ ESS	Conclusion
			STR1VE-US)	(yes/no), baseline feeding issues (yes/no), baseline CHOP-INTEND score.		
No permanent ventilation at age 14 months	Type 1	Unanchored MAIC	OA (STR1VE-EU and STR1VE-US)	Sex, age at screening, age at symptom onset, weight, SMN2 copy number, baseline ventilation support (yes/no), baseline feeding issues (yes/no), baseline CHOP-INTEND score.	CS3A and CS3B:79/31.89	████████████████████ ████████████████████ ████████
Overall survival at age 18 months	Type 1	Unanchored MAIC	OA (STR1VE-EU and STR1VE-US)	Sex, age at screening, age at symptom onset, weight, SMN2 copy number, baseline ventilation support (yes/no), baseline feeding issues (yes/no), baseline CHOP-INTEND score.	CS3A and CS3B:92/34.13	████████████████████ ████████████████████ ████████
HINE-2 sitting without support at 24 months into study	Type 1	Unanchored MAIC	Risdiplam (SUNFISH Part II)	Sex, age at screening, age at symptom onset, baseline disease duration, SMN2 copy number, baseline CHOP-INTEND score.	CS3A and CS3B:52/23.88 Note: with baseline feeding issues as a covariate ESS = 3.5	████████████████████ ████████████████████ ████████
HINE-2 stands with support at 24 months into study	Type 1	Unanchored MAIC	Risdiplam (SUNFISH Part II)	Sex, age at screening, age at symptom onset, baseline disease duration, SMN2	CS3A and CS3B: 52/23.88	████████████████████ ████████████████████ ████████

Outcome	Population	Analysis Type	Comparator	Covariates	Sample size/ ESS	Conclusion
				copy number, baseline CHOP-INTEND score.	Note: with baseline feeding issues as a covariate ESS = 3.5	
HINE-2 walks alone at 24 months into study	Type 1	Unanchored MAIC	Risdiplam (SUNFISH Part II)	Sex, age at screening, age at symptom onset, baseline disease duration, SMN2 copy number, baseline CHOP-INTEND score.	CS3A and CS3B: 52/23.88 Note: with baseline feeding issues as a covariate ESS = 3.5	
Overall survival 12 months into study	Type 1	Unanchored MAIC	Risdiplam (SUNFISH Part II)	Sex, age at screening, age at symptom onset, baseline disease duration, SMN2 copy number, baseline feeding issues, baseline CHOP-INTEND score.	CS3A and CS3B: 92/28.11	
HFMSE baseline to 12 months	Type 2/3	STC	Risdiplam (SUNFISH Part II)	Sex, age at screening, age at symptom onset, SMN2 copy number, baseline RULM score, baseline HFMSE score.	STC performed as MAIC was not feasible because it failed to match covariates	
RULM baseline to 12 months	Type 2/3	STC	Risdiplam (SUNFISH Part II)	Sex, age at screening, age at symptom onset, SMN2 copy number, baseline	STC performed as MAIC was not feasible because it	

Outcome	Population	Analysis Type	Comparator	Covariates	Sample size/ ESS	Conclusion
				RULM score, baseline HFMSE score.	failed to match covariates	
Abbreviations: BSID-III = Bayley Scales of Infant and Toddler Development, Third Edition; CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; ESS = Effective Sample Size; HFMSE = Hammersmith Functional Motor Scale (expanded); HINE-2 = Hammersmith Infant Neurological Examination - Part 2; MAIC = matching-adjusted indirect comparison; OA = onasemnogene abeparvovec; RULM = Revised Upper Limb Module; SMN2 = Survival Motor Neuron 2; STC = simulated treatment comparison; WHO MM = World Health Organization Motor Milestones						

6.2.5 Critique of Biogen MAA

6.2.5.1 Paediatric registry

The paediatric registry updated the following items in April 2025:

- WHO MM information
- Mixed model for repeated measure (MMRM) analysis for HINE-2 in SMA type 1,
- Responders analysis (defined as an increase in 1 point on HINE and 9 points on CHOP-INTEND)
- Number of patients with permanent ventilation
- Number of patients requiring tracheostomy
- Overall survival
- EK-2 overview

Data for WHO MM was provided over time, with number of patients per SMA type who improved or maintained motor function reported. Additional analyses were conducted using linear interpolation, when patients had missing data, based on the patients' observed data at flanking visits.

In the original report, MMRMs were conducted for the following outcomes and SMA types:

- CHOP-INTEND: type 1, including an analysis splitting patients by those were expanded access programme (EAP) and non-EAP
- RHS: type 2/3
- RULM: type 2/3
- RHS/CHOP-INTEND: type 1, analysis for those initially measured on CHOP-INTEND but baseline was redefined to RHS after ceiling effect reached on CHOP-INTEND, or patient achieved skills not measured by CHOP-INTEND (i.e. rolling and sitting)
- RULM/CHOP-INTEND: type 1, analysis for those initially measured on CHOP-INTEND but baseline was redefined to RULM for children age ≥ 2.5 years old, who can sit (supported/unsupported) and have functional use of their upper limbs

MMRM models include the following covariates:

- Baseline score
- SMA type 2/3 – where appropriate
- Baseline function (non-sitters, sitters, walkers) – although this is confounded with baseline score
- Weight at baseline visit
- Age at symptom onset (month)
- Age at treatment initiation (years)
- Duration of disease at baseline visit: age of diagnosis to age at treatment initiation (years)
- Time between treatment initiation and baseline visit (days)

Age of diagnosis was preferred to age of symptom onset, as this does not rely as often on patient recall.

Descriptive data was also provided for RHS timed tests (10 metre run test and rise from floor test). MMRM was not feasible for these outcomes.

Over the original and updated reports, MMRM were conducted when feasible (i.e. there was enough data). In cases of insufficient data, results are generally reported narratively and tabulated (e.g. means and SDs). Not all outcome provided are mandated (e.g. EK-2) but are still provided, with the caveat that data cleaning was not as thorough for MAA mandated items.

Overall, the analyses of the data are conducted when plausible and the limitations of the data are clearly highlighted within the report.

The following PROMs outcomes were also reported (December 2023 report):

- Patient global impression of severity score (PGI-S); higher value is worse
- Patient global impression of improvement score (PGI-I); higher value is worse
- SMA independence scale (SMAIS); higher values equate to higher independence
- EQ-5D-5L/EQ-5D-Y; higher values indicate more problems; visual analogue scale (VAS, 0-100); higher value indicates better health

As patient numbers were low and data lacked maturity, only descriptive statistics are presented. The EAG consider this appropriate.

6.2.5.2 *Adult registry*

The adult registry updated all analyses from the original report (April 2024) therefore, the new (April 2025) report is to be considered here. Data was presented for the following:

- WHO MM information
- MMRM for ATEND (left and right)
- MMRM for EK2
- MMRM for RULM
- MMRM for RHS
- MMRM for 6 Minute Walk Test (6MWT)

MMRMs were adjusted for the following baseline covariates:

- Patient (random effect)
- Age at symptom onset (fixed effect)
- Age at treatment initiation (fixed effect)
- SMA type (fixed effect)
- Treatment duration at time of visit (fixed effect)
- Disease duration (age at treatment state minus age at symptom onset; fixed effect)

To increase data availability, the registry removed the requirement for at least one follow-up score and weight as a covariate. Removal of the criterion of at least one follow-up score increased both the number of patients and value of data (i.e. scores) contributing to the models. Weight was not used due to a large amount of missing data. The previous report (April 2024) included baseline score, baseline-visit interaction, and baseline motor function; reasons for not including these in the updated report are not explicitly stated. The previous report also included a sensitivity analysis for patients naïve to treatment and pre-treated patients. Additionally, the updated report (April 2025) split by status (i.e. non-sitters, sitters, and walkers), whereas the previous report (April 2024) assessed type 2/3 patients as a whole. The new report therefore offers more granularity in terms of subgroups of SMA type 2/3 patients but does suffer from smaller patient sample sizes. When patient numbers are below five, no results are calculated for that follow-up period.

Overall, the analyses are conducted using appropriate methods and attempts have been made to provide context to the results and consider type 2/3 patients as separately as possible.

6.2.6 Results of Biogen SLR

Two phase III, randomised controlled trials of nusinersen versus sham procedure have been conducted for patients with type 1 SMA (ENDEAR),²⁷ and type 2/3 SMA (CHERISH) respectively.²⁸ For patients who were not eligible for these trials, a phase II randomised trial was available (EMBRACE).²⁹ The part 1 randomised element of EMBRACE finished early and patients were offered the opportunity to transition to the open-label extension. There is no randomised evidence for presymptomatic patients, only a single arm study that treated genetically diagnosed infants in the first six weeks of life (NURTURE).³⁰ These studies, plus relevant dose-finding studies and the open-label extension study that enrolled types 1, 2 and 3 patients from the other studies (SHINE), are shown in Table 10.

Table 10: Overview of clinical effectiveness evidence for nusinersen (reproduced from Biogen submission table 5)

Study	NURTURE	CS3A	ENDEAR	CS2/CS12	CHERISH	EMBRACE	SHINE
Study design	Phase II, open-label, multicentre, single-arm study	Phase II, open-label, multiple dose, single-arm, multicentre study	Randomised, double blind, multicentre (including UK), phase III, sham-procedure controlled	CS2: Phase I/IIa, open-label, multicentre, multiple-dose, dose escalation study CS12: Phase I, multicentre, open-label, multiple-dose extension study	Randomised, double-blind, multicentre, phase III, sham-procedure controlled	Phase II, randomised, double-blind, sham-procedure controlled study	Open-label extension study
Population	Presymptomatic infants genetically diagnosed with SMA (likely to develop early or later onset SMA)	Symptomatic infantile-onset (type 1) SMA	Symptomatic infantile-onset (type 1) SMA	Symptomatic later-onset (type 2/3) SMA	Symptomatic later-onset (type 2/3) SMA	Patients with SMA who are not eligible to participate in ENDEAR and CHERISH	Patients who participated in the initial studies (ENDEAR, CHERISH, EMBRACE, CS3a, and CS12)
Intervention(s)	Nusinersen (N=25)	Nusinersen (N=21)	Nusinersen (N=80)	Nusinersen (N=34 in CS2 and N=47 in CS12)	Nusinersen (N=84)	Nusinersen (N=14)	Nusinersen (N=327)
Comparator(s)	None	None	Sham procedure (N=41)	None	Sham procedure control (N=42)	Sham procedure (N=7)	None

Study	NURTURE	CS3A	ENDEAR	CS2/CS12	CHERISH	EMBRACE	SHINE
Indicate if study used in the economic model	Yes	No, phase III data is available from ENDEAR	Yes	No, phase III data is available from CHERISH	Yes	No	Yes

Participation in ENDEAR was limited to those with two SMN2 copies, with SMA symptom onset within the first six months but not the first week of life. For CHERISH, participants had to be between 2-12 years and able to sit but not walk independently; they were excluded from the trial if they had a gastric feeding tube, severe contractures or scoliosis, or needed ventilation for more than six hours during a 24-hour period. Participants in CHERISH only received three loading doses of nusinersen with a maintenance dose after six months, whereas ENDEAR participants received the recommended four loading doses plus maintenance doses after four months. It should be noted, then, that the CHERISH trial is not generalisable to UK clinical practice because participants did not receive the relevant dose, and because of restrictions in eligibility around age, complications and ventilation requirements.

The company reported that none of the presymptomatic patients had died or required permanent ventilation by a median age of 4.9 years (range 3.8 to 5.5 years), compared to an estimated average age of mortality from natural history of 19.2 months (SD 10.1 months).²⁰ Children with three SMN2 copies were walking independently within normal developmental timeframes; 13 of the 15 children with two SMN2 copies achieved the WHO motor milestone of standing alone and walking alone, whilst 14 achieved hands and knees crawling and walking with assistance, and all achieved sitting without support and standing with assistance. A total of 88% of children achieved the maximum CHOP-INTEND score, and mean HFMSE scores showed continuous improvement.

For type 1 patients, the nusinersen group showed a 62.8% reduction in the risk of death and a 47% reduction in risk of death or permanent ventilation compared to the sham group. They showed progressive mean increases in motor function according to WHO motor milestones, HINE-2 and CHOP-INTEND. Fewer patients discontinued treatment in the treatment group than the sham group, for reasons not attributed to the treatment.

For type 2/3 patients, most on nusinersen experience clinically meaningful and statistically significant increase in motor scores (WHO motor milestones, HFMSE and RULM) at 15 months.

Results of the extension studies suggest that longer term treatment is beneficial; [REDACTED]

The company reported a favourable safety profile. The most reported AEs were headache, vomiting, and back pain, and were attributed mostly to the administration of the drug via lumbar puncture.

An evaluation of the risk of bias in these studies can be found in section 13.2.

6.3 Critique of Biogen economic models

The EAG reviewed and critically appraised the economic models and the additional information in response to the points for clarification submitted by Biogen.^{31,32} In this section, we assess the company submission against the NICE reference case checklist³³ and then we present a critique of the submitted economic model structures and the economic evidence used to parameterise these economic models according to the population groups defined in the decision problem (presymptomatic, type 1 and type 2/3 SMA).⁶

6.3.1 NICE decision problem

The company submission was evaluated against the NICE reference case checklist³³ and the findings are summarised in **Table**.

Table 11: Comparison of company's and NICE decision problem

Element of health technology assessment	Reference case (based on NICE scope/methods)	EAG comment on company's submission
Defining the decision problem	People with types 0, 1, 2, 3 or 4 5q SMA, or presymptomatic 5q SMA confirmed with genetic testing with 1 to 4 SMN2 copies	The company submission did not report on type 0 and 5q SMA type 4 because of paucity of evidence to conduct an economic evaluation. The company reported the economic evaluation results separately for presymptomatic SMA, along with subgroup analysis for 2 SMN2 gene copies SMA and 3 SMN2 gene copies SMA subpopulations; type1 SMA and type 2/3 SMA populations.
Intervention	Interventions are monotherapies in addition to existing clinical services and established clinical management.	The company assessed the cost-effectiveness of nusinersen.
Comparators	Established clinical management in the NHS, including the Best supportive care (BSC) The interventions will be compared to each other In addition, Onasemnogene Apeparvovec (OA) will be used as comparator treatment for children aged 12 months and under with a bi-allelic mutation in the SMN1 gene and present with a clinical diagnosis of type 1 5q SMA or presymptotically with up to 3 copies of the SMN2 gene.	Because of lack of evidence, the company did not consider risdiplam and OA appropriate comparators against nusinersen for economic analysis. OA was not an appropriate comparator for type 2/3 SMA population and not considered.
Perspective on outcomes	The outcome measures to be considered include:	Presymptomatic model: Nusinersen: WHO motor milestone achievement from NURTURE ^{30,34} .

Element of health technology assessment	Reference case (based on NICE scope/methods)	EAG comment on company's submission
	• Motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills) • Bulbar function (including, for example, swallowing and ability to communicate) • Frequency and duration of hospitalisation • Respiratory function • Complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation • Stamina and fatigue • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers)	BSC: weighted average of relative efficacy from ENDEAR²⁷ and CHERISH²⁸ Type 1 SMA model: Nusinersen: a combination of HINE-2 (aged two or less) and WHO motor milestone (above age 2) achievement data from ENDEAR²⁷ and SHINE BSC: HINE-2 motor milestones from sham control arm of ENDEAR²⁷ Mortality data also informed by ENDEAR²⁷ and SHINE³⁵. Type 2/3 SMA model: Nusinersen: WHO motor milestones data from CHERISH²⁸ and SHINE³⁵ BSC: WHO motor milestones from CHERISH²⁸ Mortality data informed by Wijngaarde et al. 2020³⁶ and general population mortality Bulbar dysfunction, non-permanent respiratory support, scoliosis, stamina and fatigue impact not considered separately because of data limitations.
Perspective on costs	Costs will be considered from an NHS and Personal Social Services perspective.	Appropriate
Type of economic evaluation	Cost utility analysis	Cost utility analysis was conducted comparing nusinersen against BSC.
Time horizon	The reference case stipulates that the time horizon for estimating clinical and cost	100-year time horizon covering the lifetime of the patient.

Element of health technology assessment	Reference case (based on NICE scope/methods)	EAG comment on company's submission
	effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	
Synthesis of evidence on health effects	Based on systematic review	Presymptomatic model: Weighted average of relative risk of no treatment response from CHERISH²⁸ and ENDEAR²⁷ Type 1 SMA model: Health effects measure taken from ENDEAR²⁷ and SHINE³⁵ Type 2/3 SMA model: Health effects measure taken from CHERISH²⁸ and SHINE³⁵
Measuring and valuing health effects	Express health effects in QALYs for cost-effectiveness analyses.	Appropriate
Source of data for measurement of health-related quality of life	For the reference case, report the measurement of changes in health-related quality of life directly from patients.	HST24 ¹⁶ and carer HSUVs from TA588 ²
Source of preference data for valuation of changes in health-related quality of life	The utility of these changes should be based on public preferences using a choice-based method.	Appropriate
Equity considerations	No additional equity considerations in the NICE scope.	Appropriate
Evidence on resource use and costs	Resource use and cost data should have been identified systematically	Resource use and cost data informed by the HST24 ¹⁶ were inflated to price year 2021/22.
Discounting	Annual discount rate of 3.5% for costs and outcomes.	Appropriate
Source: ^{31,33}		

Element of health technology assessment	Reference case (based on NICE scope/methods)	EAG comment on company's submission
Abbreviations: BSC, best supportive care; EAG = Evidence Assessment Group; HSP = highly specialised technologies; OA = Onasemnogene Apeparvovec; SMA = spinal muscular atrophy, SMN= survival motor neuron; QALY = quality-adjusted life year		

6.3.2 Presymptomatic SMA population

6.3.2.1 Model structure

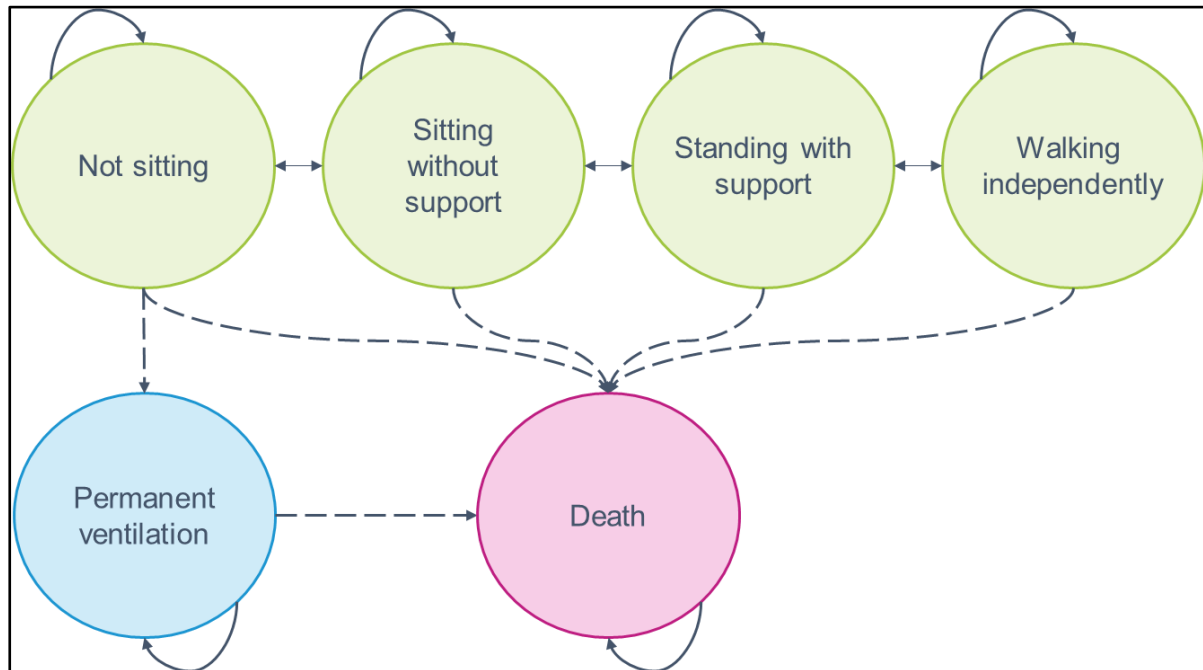
6.3.2.1.1 Type of model

Biogen used a Markov model to represent the natural history of presymptomatic 5q SMA which was primarily informed by the previous NICE TA588² for nusinersen (Figure 1). Both the models for presymptomatic and type 1 population had the same structure.

6.3.2.1.2 Health states and transitions

The Markov model was built in Microsoft Excel with 6 health states: 'not sitting', 'sitting without support', 'standing with support', 'walking independently' based on the highest mobility milestone attained, 'permanent ventilation' and 'death'.³¹ All states were based on gross motor milestones clinically defined using WHO motor milestones (WHO MM),³⁷ except for 'permanent ventilation' and 'death'. All patients started in the 'not sitting' state, in part due to the baseline age of the presymptomatic patient cohort (mean [REDACTED]) in the NURTURE trial, and could transition to another health state or remain in the same health state after each model cycle (4 months).³¹ It was assumed that only patients in the 'not sitting' health state could transition to the 'permanent ventilation' health state defined in line with the NURTURE trial as: requiring a tracheostomy or having at least 16 hours of ventilatory support per day for more than 21 days.³¹ Once patients reached this latter health state it was assumed they could not improve and therefore remained in that state until they die (absorbing state).³¹

Figure 1. Model structure for presymptomatic and type 1 SMA populations used by Biogen



Source: Biogen CS Section B 3.2.2, Figure 35³¹

Abbreviations: SMA = spinal muscular atrophy

The health state occupancy for patients receiving nusinersen were informed by the ongoing NURTURE trial³⁰ with an expected follow-up of 72 months (6 years) (see Table 12 below). In the points for clarification letter³² the company confirmed that the outcome measures using HINE-2 from NURTURE³⁰ informed model state occupancy over the first 24 months. The WHO MM³⁷ data from NURTURE was used to inform state occupancy after 24 months. The company assumed equivalence between motor milestones as defined by HINE-2, and the health states in the economic model defined by WHO MM³⁷. The company assumed equivalence between motor milestones as defined by HINE-2 and the health states in the economic model defined by WHO MM.³⁷ The definitions for motor milestones are reported in Table 13.

Table 12: HINE-2 and WHO motor milestones that informed model state occupancy for nusinersen

Time point	Not Sitting	Sitting without support	Standing with support	Walking independently
Total population				
Baseline	■	■	■	■
Month 6	■	■	■	■
Month 9	■	■	■	■
Month 12	■	■	■	■
Month 15	■	■	■	■
Month 18	■	■	■	■

Time point	Not Sitting	Sitting without support	Standing with support	Walking independently
Month 24	■	■	■	■
Month 36	■	■	■	■
Month 48	■	■	■	■
Month 60	■	■	■	■
Month 72	■	■	■	■
Source: Biogen CS Section B 3.3.1, Table 39 ³¹ Abbreviations: HINE-2 = Hammersmith Infant Neurological Examination – Part 2				

Table 13: Comparison of motor milestone definitions for HINE-2 and WHO motor milestone measures

Model health states	HINE-2 definitions	WHO motor milestones
Not sitting	<3 in the HINE-2 sitting dimension	-
Sitting without support	Score 3-4 in sitting ability (stable sitting or pivot achievement) and a score of less than 2 in standing ability.	Sits up straight with head erect for 10 seconds without support from hands.
Standing with support	Score of 2 in standing ability. Any score in other items except walking ability.	Stands in an upright position on both feet holding onto a stable object with support from hands only for 10 seconds. The body does not touch the stable object.
Walking independently	Score of 3 in walking ability. Any score in other items.	5 steps independently. One leg moves while the other supports weight.
Source: Biogen CS Section B 3.2.2, Table 34 ³¹ Abbreviations: HINE-2 = Hammersmith Infant Neurological Examination – Part 2; WHO = World Health Organization		

At 6 years of age (corresponding to the last assessment time point in NURTURE),^{30,34} patients receiving nusinersen treatment were assumed to either retain or decline their motor milestone for the remainder of their lives. Patients could only lose one motor milestone per model cycle, and the risk of decline for patients receiving nusinersen was relative to the risk of decline from BSC. Patients receiving nusinersen were assumed to have no risk of progression to 'permanent ventilation' based on results from NURTURE.³⁰

State occupancy for BSC (Table 14) was based on a weighted average of data from the BSC arms of the ENDEAR²⁷ and CHERISH²⁸ trials with a follow-up of 15 months, a pragmatic choice following the fact that NURTURE³⁰ is a single-arm trial. SMA types were weighted based on a disease distribution from Calucho et al.³⁸ After the points for clarification³², the company further detailed that the primary outcome in ENDEAR²⁷ used HINE-2, hence the

model assumed equivalence between HINE-2 scores and model milestones (see Table 13 to see how model states are defined according HINE-2 scores and WHO motor milestones).³⁷

Table 14: Model state occupancy for the BSC

Time point	Not Sitting	Sitting without support	Standing with support	Walking independently
Total population				
Baseline	■	■	■	■
Month 6	■	■	■	■
Month 9	■	■	■	■
Month 12	■	■	■	■
Month 15	■	■	■	■
Source: Biogen CS Section B 3.3.1 Table 42 ³¹ Abbreviations: BSC = best supportive care				

Since participants in the CHERISH²⁸ trial were older than those in ENDEAR²⁷, they reached mobility milestones earlier. Thus, applying these state occupancy data directly to the patients receiving BSC in the presymptomatic model would have led to implausible levels of motor milestone attainment. The company therefore adjusted the level of motor milestone attainment by type 2 and 3 patients in CHERISH²⁸ trial by up to two health states, thereby increasing the time to achieve motor milestones. For example: in patients with SMA type 3 attaining 'walking independently' at 6 months post baseline (baseline age of 5.29 months), the adjustments would mean that the patients attain this milestone at 15 months post baseline (assumed age of ■ at baseline for presymptomatic population).

After 15 months (1.25 years) of receiving BSC, patients were assumed to retain or decline their motor milestone by a maximum of one milestone per cycle. The risk of decline was constant over time, based on Wadman et al.³⁹ and varied by health state and type SMN2 gene subgroup. It was assumed that only the patients in the 'not sitting' state had the probability to transition to 'permanent ventilation'. The risk of BSC patients moving to permanent ventilation was constant over time and was based on estimates by Wijngaarde et al.³⁶ and in line with the approach taken in HST24.¹⁶

EAG comment: The EAG is satisfied that the model structure used by the company to assess the cost-effectiveness of nusinersen versus BSC captures the costs and benefits appropriately. However, the EAG highlights some potential issues in the following sections. The HINE-2 outcome measure was collected in the NURTURE³⁰ trial informing clinical effectiveness of nusinersen treatment and is considered more comprehensive than the WHO MM for its inclusion of voluntary grasp and head control. These differences between the measures could have impacted the state occupancy and ultimately the number of patients at risk of 'permanent ventilation'. Therefore, assuming equivalence between the HINE-2 and WHO MM during the early stages of treatment could have potentially introduced structural uncertainties in the presymptomatic model.

The EAG understands there is a lack of data on patients with presymptomatic SMA receiving BSC however, cautions that adjustments to the state occupancy for patients receiving BSC in the presymptomatic model, which are derived from the level of motor milestones within two

health states attained patients with type 2 and 3 in the CHERISH²⁸ trial, could have potentially favoured nusinersen.

6.3.2.2 Population

The population considered in the presymptomatic model reflected that of the NURTURE³⁰ baseline characteristics (Table 15).

Table 15: Baseline population characteristics in the presymptomatic model

Characteristics	Total presymptomatic population	Two copies of SMN2	Three copies of SMN2
Baseline age in years (mean (SE))			
Sex (female %)			
Baseline weight in kg (mean (SE))			

Source: Biogen CS Section B 3.3.1 Table 36³¹

Abbreviations: SE= standard error; SMN = survival of motor neuron

EAG comment: The EAG considers the company's consideration of the population (total presymptomatic, two SMN2 copies, three SMN2 copies) in their model appropriate.

6.3.2.3 Interventions and comparators

The presymptomatic model compared nusinersen against BSC in a population with the characteristics reported in Table 15.

Intervention: The company modelled nusinersen as the first-line therapy according to its marketing authorisation as treatment. In the economic model, in line with the marketing authorisation, the patient cohort receiving nusinersen were administered four loading doses of 12 mg nusinersen in the first four-month cycle, and then in the subsequent cycles, the cohort received one maintenance dose of 12 mg nusinersen per cycle.³¹ All ages received the same dose which was administered intrathecally.

Comparator: The company modelled BSC as the comparator across all populations and reflected the mix of gastrointestinal, respiratory, nutritional and orthopaedic interventions delivered by a multidisciplinary team. The company did not compare nusinersen against risdiplam or OA because of poor availability of data; and the results from the ITC had major limitations and were not considered appropriate.

EAG comment: Biogen's decision problem assumes that patients diagnosed with presymptomatic SMA receive nusinersen, while those with a missed presymptomatic diagnosis receive BSC without access to a disease-modifying therapy. However, following consultation with the company, the EAG found little evidence to support the idea that a presymptomatic diagnosed patient would be excluded from receiving any available disease-modifying therapy. Based on both the clinical context and the evidence available, the EAG cautions against the use of BSC as an appropriate comparator in the presymptomatic SMA population. In addition, all studies involving presymptomatic population were single-arm, and the EAG notes that the company model relied on strong assumptions of outcomes under BSC.

Nevertheless, the current NICE scope does not specify whether BSC is an appropriate comparator for all the SMA types⁶, and the EAG also recognises the broader data limitations for BSC and other treatment comparators such as OA and risdiplam.

6.3.2.4 *Perspective, time horizon and discounting*

The analysis was conducted from the perspective of the NHS and Personal Social Services and with a time horizon of 100 years in the base case. The costs and benefits were discounted at annual rate of 3.5%.

EAG comment: The EAG considers the approach taken in the company model appropriate and in line with the NICE guidelines⁴⁰. The 100-year time horizon is long enough to capture the costs and benefits of treatment received over the average lifetime of the patients.

6.3.2.5 *Treatment effectiveness and extrapolation*

The evidence of treatment effectiveness for nusinersen used in the presymptomatic model was informed by the NURTURE trial.^{30,34} The model used the WHO MM outcomes over the first 72 months directly from NURTURE (see section 6.3.2.1.2). Relative estimates of efficacy for nusinersen versus BSC were not available from single-arm trials including NURTURE.^{30,34} Therefore, in the absence of long-term data, the relative efficacy estimates from the ENDEAR²⁷ (for type 1 SMA) and CHERISH²⁸ (for type 2/3 SMA) trials were used in the presymptomatic population to estimate the risk of decline in the nusinersen cohort.

The company presented an unanchored MAIC between nusinersen and OA for the presymptomatic population using endpoints for WHO MM 'standing with support' and 'walking independently'.³¹ The results of this analysis were not used in the economic model. The reasons that the company provided included assessment timelines that did not align for the clinical outcomes and small sample sizes from the study population of each treatment.

EAG comment: On the relative risk of decline calculation, the EAG is concerned that this approach pools estimates of relative risk with different clinical definitions without adequately acknowledging the limitations of this approach. It is also worth noting that there was no evidence of difference (not statistically significant) in the risk difference between nusinersen and BSC treatment response in CHERISH.²⁸ Additionally, the analysis conflates the clinical definitions, treating lack of milestone improvement equivalent to motor milestone decline, which may introduce uncertainty. However, the EAG acknowledges the limited availability of data. In addition, the EAG finds the company's justification for not using unanchored MAIC results to compare nusinersen vs OA appropriate. Nevertheless, the EAG explored a comparison between nusinersen vs OA using the unanchored MAIC results despite being poor in terms of data.³¹

6.3.2.6 *Health related quality of life*

Utilities were based on the most recent NICE appraisal for treating presymptomatic SMA, HST24.¹⁶ Age and gender adjustments to utilities have been made using a multiplicative approach following NICE guidelines. Utility values depended on model health-state. An on-treatment utility increment of 0.1 (based on clinical expert opinion) was also included for all patients while they received nusinersen, which allowed accommodation of any additional gains in health-related quality of life (such as additional upper limb function) that were not captured in the health state utility values. The same set of health-state related utility values were used across all models regardless of the SMA types and regardless of treatment (Table

16). In a scenario analysis, the company considered the health-state utility values used as an exploratory analysis by a previous EAG in TA755 for treatment of SMA with risdiplam.³

Table 16: Health state utility values used in the company base-case models

Health state	Utility
Permanent ventilation	0
Not sitting	0.19
Sitting	0.6
Standing	0.77
Walking	Equivalent to general population
Additional utilities	
Treatment benefit	0.1
Source: Biogen CS Section B 3.4.5 Table 62 ³¹	

6.3.2.7 Approach to care-giver health-related quality of life

The company adopted a utility increment approach for care givers based on model health states. The model further assumes that carer utility values depend on the model health state and not on the SMA type or the treatment received (i.e. carer utilities only increase with the attainment and maintenance of motor milestones regardless of treatment or SMA type). Therefore, the company used the same carer utility values across the models. The approach was based on EAG feedback from TA755.³ The company did not conduct any scenario analyses using alternative carer utility values. It was assumed that there would be 1 carer for each SMA patient across health states (initial 2 carers corrected by the company in the addendum; see Table 17).

Table 17: Health state utility values for carers and the number of carers used in company base-case models

Health state	Number of carers	Utilities
Permanent ventilation	1	0.484
Not sitting	1	0.484
Sitting without support	1	0.628
Standing with assistance	1	0.771
Walking independently	1	Population norm
Source: Biogen CS Section B 3.4.5 Table 62 ³¹		

EAG comment: The EAG considers the health state utility values used in the company models appropriate. The EAG acknowledges that patients can get improvements in quality of life within each motor milestone (e.g. holding objects, lifting toys, or simply being able to sit for few secs etc) and these nuanced benefits may not be adequately captured by the generic preference-based measure (EQ-5D-3L). The importance of these subtle improvements in quality of life have been raised in the EAG's engagement with patients and professionals. (see section 13.5)

The EAG acknowledges the importance of including the experience of informal carers in this appraisal; however, there are no standardised methodologies to quantify the impact on health-

related quality of life from informal carers, and the data specific to SMA is scarce. Therefore, in the EAG base-case, models focussed primarily on the quality of life of patients. The data for informal carers were used and presented as an additional scenario for the purposes of transparency, allowing an explicit assessment of the disease burden for patients alone, and for patients and their carers together.

6.3.2.8 Resource use and costs

The company used a list price of £75,000 per 12mg/5ml vial of nusinersen plus an administration cost of the drug (£836 per dose, assumed as a proxy for diagnostic spinal puncture). However, after applying a PAS of [REDACTED] the acquisition cost of nusinersen were reduced to [REDACTED] per dose. No concomitant medication costs were applied into the economic model.

The company did not apply additional drug acquisition cost, administration or concomitant costs for BSC.

The company used the healthcare resource utilisation costs that were previously used in the NICE appraisal of OA (HST24¹⁶) (Table 18). In the absence of costs for the “standing” health state, the company assumed them to be equivalent to the “walking” health state. In addition, the company used alternative health state costs from the previous NICE risdiplam appraisal (TA755)³ in the scenario analyses (

Table 19).

Table 18: Health care resource utilisation costs applied to the health states in the company models

Resource category	Permanent ventilation	Non-sitter	Sitting	Standing and Walking
Drugs	£619	£810	£781	£1,012
Medical tests	£880	£1,152	£917	£675
Medical visits	£3,669	£4,801	£2,805	£2,461
Hospitalisations	£218,987	£70,829	£40,577	£276
Accident and Emergency	£375	£490	£201	£80
Health material	£3,590	£4,400	£2,274	£652
Social services	£55,590	£30,019	£20,013	£3,177
Total	£283,710	£112,500	£67,567	£8,333
Source: Biogen CS Section B 3.5.2 Table 65 ³¹				

Table 19: Alternative health care utilisation costs applied to health states in the company models

Health state	Annual cost reported in TA588 ²	Inflated annual cost (applied in CEM) [¥]	Inflated cost per 4-month cycle
Permanent ventilation*	£136,444	£150,989	£50,330
Not sitting	£77,968	£86,280	£28,760
Sitting	£55,185	£61,068	£20,356
Standing	£20,229	£22,385	£7,462
Walking	£20,229	£22,385	£7,462
* The annual cost for 'permanent ventilation' is assumed to be equivalent to the cost of 'not sitting' as per TA588² with a 175% increase in costs as applied in TA755³ ¥ Costs are inflated from cost year 2016/17 to 2021/22 using an inflation index of 1.11 using indices derived from PSSRU 2022, NHSCII pay and prices., PSSRU: Personal Social Services Research Unit, NHSCII: NHS cost inflation index Abbreviations: CEM, cost-effectiveness model			

EAG comment: The EAG considers the company's estimate of resource utilisation and health states costs appropriate.

6.3.2.9 Adverse events

There were no reported adverse events attributed to nusinersen for presymptomatic patients in the NURTURE³⁰ trial. The company did not apply adverse events and associated costs/utility decrements into their economic models. There were no other additional costs applied into the models. As a justification for not including the treatment related adverse events, the company referred to TA588,² TA755³ and HST15,⁴¹ where the impact of any adverse events was not explicitly incorporated into the economic model as they were considered to be accounted already by the health state utility values given the nature of SMA.

EAG comment: The EAG considers the company's approach not to incorporate any additional costs and utility impacts of treatment related adverse events into the model due to low incidence (< 5% of severe treatment-related events) aligns with previous appraisals and is appropriate. In any case, there were no adverse events attributed to nusinersen for presymptomatic patients in the trial.³⁰ However, had there been adverse events, it could be argued that incorporating them into the model would have led to the double counting of associated impact.

6.3.2.10 Survival

The company did not use the survival data from NURTURE to inform the nusinersen cohort in the presymptomatic model because all patients were alive with a mean age of 4.9 years and had no permanent ventilation at the data cut-off. Therefore, the company utilised the digitised version of the appropriate parametric curves from HST24¹⁶ for 'permanent ventilation', 'not sitting' and 'sitting' cohorts in the model states. The mortality estimates from 'standing without support' and 'walking independently' health states were informed by UK general population mortality data. The company used the national life tables from 2017-19 for the UK general population mortality data to minimise the impact of COVID-19 in the then available life tables from 2020-22.⁴² In the absence of comparative data, the company used the same survival data for nusinersen (across all subgroups) and BSC.

EAG comment: The EAG acknowledges the limited availability of data and considers the company's approach of incorporating the health-state dependent mortality appropriate. The EAG is satisfied with the company's choice of parametric curves from HST24¹⁶.

6.3.2.11 *Discontinuation*

The company assumed that any patient who transitions to 'permanent ventilation' would discontinue nusinersen treatment because of inability to undergo the intrathecal administration needed. The company utilised the Managed Access Agreement (MAA)¹⁸ data to inform discontinuation of treatment for reasons other than permanent ventilation. There were insufficient data to estimate the discontinuation rates using the MAA data for presymptomatic population. However, due to the similar prognosis between presymptomatic SMA and type 2/3 SMA, the company used MAA discontinuation results for nusinersen in the SMA 5q type 2 and 3 populations. In the absence of data from MAA, discontinuation data from the 'walking independently' health state was applied to the 'standing with support' health state. Discontinuation rates were applied over time and differed by model health state but not by sub-population. The company assumed that after discontinuation, the cohort moved on to receive BSC and incurred costs and outcomes specific to BSC.

EAG comment: The EAG acknowledges the limitations in the available data and considers the company's approach in incorporating discontinuation appropriate. However, it is likely that those discontinuing nusinersen may not transition to receive BSC alone, but instead may receive alternative disease modifying treatments. This would have implications for both the costs and outcomes, which are not fully captured in the current models.

6.3.2.12 *Decision modifier: Severity*

The company included carer utilities in the base-case analysis, and in line with the TSD23⁴³ recommendation, did not include a severity modifier when carer utility increments were applied. However, severity modifiers were included in the scenario analyses where carer utility increments were removed. A highest QALY shortfall of 1.7 was applied to the type 1 model, and 1.2 was applied to the presymptomatic model, whereas no QALY shortfall was applicable to the type 2/3 model.

EAG comment: The EAG considers the company's approach of incorporation of severity modifier in QALYs gains in treatment of SMA to be appropriate, given the severity of the condition. However, the EAG cautions that applying a severity modifier may risk double counting if the health state utility values used to calculate the QALYs already reflect disease severity. Therefore, for transparency and explicit assessments the EAG assessed the impact of incorporating the severity modifier only as an additional analysis presented alongside the base-case.

6.3.2.13 *Company's cost-effectiveness results (presymptomatic SMA population)*

The company reported both the deterministic and probabilistic results, and the deterministic sensitivity analysis and scenario analyses results. The base-case results are based on the analysis which included carer utilities and considered the PAS discounted price for nusinersen.

Based on the updated results presented in the company response to the points for clarification (March 2025),³² in the base-case analysis, nusinersen [REDACTED] over BSC with an ICER of [REDACTED] Table 20). The probabilistic results were generally stable. Nusinersen had a [REDACTED] probability of being cost-effective compared to BSC at a £30,000/QALY willingness to pay threshold.

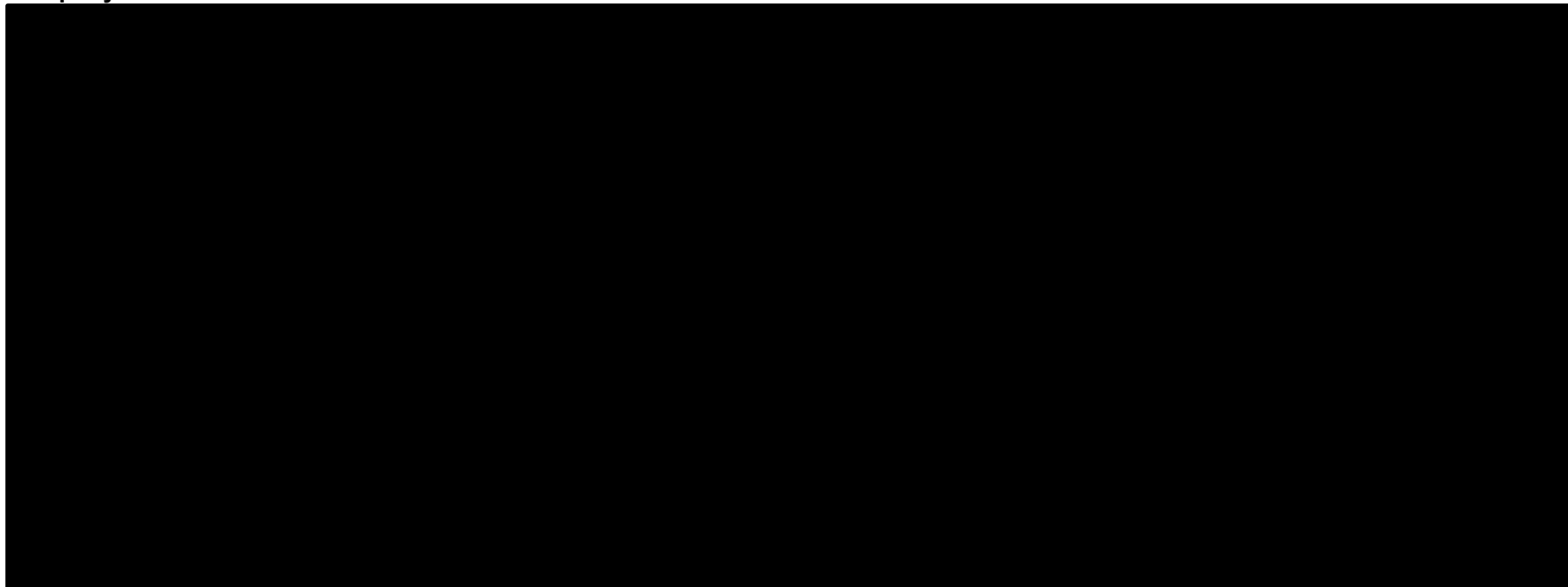
Table 20: Deterministic and probabilistic results for presymptomatic population reported by the company (using nusinersen PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB at £30,000/QALY
Deterministic								
Nusinersen	████████	20.88	██████	-	-	-	-	-
BSC	████████	19.91	██████	████████	0.97	8.32	████████	████████
Probabilistic								
Nusinersen	████████	20.93	██████	-	-	-	-	-
BSC	████████	19.92	██████	████████	1.01	8.26	████████	████████
<i>Probability cost-effective</i>								██████
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LYG = life years gained; NHB = net health benefit; QALYs = quality-adjusted life years								
Source: originally reported in Biogen CS Section B 3.9.1 Table 72 and Table 73 ³¹ , results updated by the company in points for clarification ³²								

6.3.2.13.1 Deterministic sensitivity analysis (presymptomatic population)

One-way sensitivity analysis conducted by the company by varying key input parameters, was reported to show that health-state costs had the highest impact on ICER, followed by relative risk of decline in the nusinersen treatment arm (Figure 2).

Figure 2: Tornado diagram showing the one-way sensitivity analyses for nusinersen on presymptomatic population reported by the company



Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years

Source: originally reported in Biogen CS Section B 3.10.2 Figure 56³¹, results updated by the company in points for clarification³²

6.3.2.13.2 Company's scenario analysis (presymptomatic population)

The company conducted a range of scenario analyses which assessed the impact caused by a change in a parameter on the base-case results (Table 21). Assuming the health state costs from TA588² increased the deterministic ICER above the £30,000/QALY threshold, while assuming no long-term decline in motor milestones for nusinersen led to it being more effective and less costly than BSC. Deterministic sub-group analyses showed that, for the subgroup with 2 copies of SMN2, nusinersen [REDACTED] than BSC in the probabilistic analysis. For the subgroup with 3 copies of SMN2 nusinersen had a deterministic ICER of [REDACTED].

Table 21: Company's scenario analyses for the presymptomatic population (Deterministic analysis)

Scenario	Scenario analysis	ICER
0	Reference	[REDACTED]
1	Assumption that nusinersen cohort does not decline	[REDACTED]
2	The rate of decline for BSC is halved	[REDACTED]
3	Remove carer utility increments	[REDACTED]
4	Remove active treatment increments	[REDACTED]
5	Remove all increments	[REDACTED]
6	Alternate utility source: TA588	[REDACTED]
7	Costs from TA588	[REDACTED]
Abbreviations: BSC = best supportive care; ICER = incremental cost effectiveness ratio Source: originally reported in Biogen CS Section B 3.10.3 Table 97 ³¹ , results updated by the company after the points for clarification ³²		

EAG comment: The EAG considers the company's presentation of cost-effectiveness results appropriate. The scenario analyses undertaken also are reasonable. However, there was a quite large increase in ICER when costs from TA588² were used, this highlights that there would be a huge impact in the cost-effectiveness driven by any uncertainties in the health state costs.

6.3.3 Type 1 SMA

6.3.3.1 Model structure

6.3.3.1.1 Type of model

Same as the presymptomatic model. See section 6.3.3.1.1.

6.3.3.1.2 Health states/events and transitions:

Biogen generated a Markov state transition model based on motor milestones for the type I SMA population. The model structure was same as the one for presymptomatic population (see Section 6.3.2.1). The motor milestones included were the same as in the presymptomatic model, that is: 'non-sitting', 'sitting without support', 'standing with support' and 'walking independently'. The model for type 1 SMA also included a 'permanent ventilation' health state. The model had all patients start in the 'not sitting' health state due to mean age at baseline

being less than 6 months. The transition to the 'permanent ventilation' state was only possible from the 'not sitting' health state.

Health state definitions were combined based on both the WHO MM³⁷ and the HINE-2 scoring measures. Patients with a minimum score of 3 in the sitting dimension of HINE-2 were assumed to be at 'sitting without support', a minimum score of 2 in the standing dimension of HINE-2 were assumed as 'standing with support', a minimum score of 3 in the walking ability of HINE-2 were assumed as 'walking independently'. This assumption was based on the evidence from the ENDEAR²⁷ trial which had a 13-month duration and focused on HINE-2 scores as a primary outcome measure. While the SHINE³⁵ study, which informed long-term effectiveness, assessed motor function using WHO MM instead of HINE-2.

After the points for clarification letter³², the company detailed their approach for defining state occupancy for the nusinersen arm, which was based on data from both ENDEAR²⁷ and SHINE³⁵ Motor function as measured by HINE-2 from ENDEAR informed state occupancy in the first 12 months from baseline, and SHINE informed the occupancy after 12 months by assuming equivalence between HINE-2 and WHO MM outcome measures. The state occupancy data used in the nusinersen arm of the type 1 model submitted by the company are reported in Table 22.

The state occupancy for the patients receiving BSC in the company model was informed by ENDEAR²⁷ (follow-up of 13 months), where the patients never achieved the ability to sit without support (see Table 22).

Table 22: Motor milestone (health) state occupancy for nusinersen defined in HINE-2 and WHO motor milestones from the combined ENDEAR-SHINE population

Time point	Not Sitting	Sitting without support	Standing with support	Walking independently
Baseline	████	████	████	████
Month 3	████	████	████	████
Month 6	████	████	████	████
Month 9	████	████	████	████
Month 12	████	████	████	████
Month 15	████	████	████	████
Month 18	████	████	████	████
Month 24	████	████	████	████
Month 36	████	████	████	████
Month 48	████	████	████	████
Month 60	████	████	████	████
Source: Biogen CS Section B 3.3.2 Table 48 ³¹				

Table 23: Motor milestone (health) state occupancy for BSC from ENDEAR

Time point	Not Sitting	Sitting without support	Standing with support	Walking independently
Baseline	████	████	████	████
Month 6	████	████	████	████
Month 9	████	████	████	████
Month 12	████	████	████	████
Source: Biogen CS Section B 3.3.2 Table 50 ³¹ Abbreviations: BSC = best supportive care				

ENDEAR²⁷ and SHINE³⁵ together had a follow-up of 60 months; after this period patients receiving nusinersen were assumed to either maintain the motor milestones gained, or risk losing one motor milestone following each model cycle. The relative risk of no treatment response between nusinersen and BSC observed in ENDEAR²⁷ was used as the relative risk of losing one motor milestone over the time horizon beyond 60 months.

State occupancy for patients receiving BSC was informed by ENDEAR²⁷ (follow-up of 13 months), after 12 months patients were assumed to either maintain the motor milestones gained, or risk losing one motor milestone following each model cycle. The baseline risk of losing motor milestones was taken from Wadman et al³⁹. and was assumed constant over time to vary by health state.

EAG comment: The EAG discussed the patient transition, and the likelihood of motor milestone decline with the clinicians and physiotherapists. Though the decline may not be constant over time and may vary with the case, the EAG acknowledges the current data limitations and difficulties in modelling them. Therefore, the EAG finds the company's approach of estimating data for state occupancy and motor milestone decline appropriate.

6.3.3.2 Population

The baseline characteristics of the patient cohort used in the type 1 SMA model reflected those of the participants in the ENDEAR²⁷ trial (see Table 24).

Table 24: Baseline population characteristics in the type 1 SMA nusinersen model

Characteristics	Total population █████
Baseline age in years (mean)	████
Sex (female %)	████
Baseline weight in kg (mean)	████
Source: Biogen CS Section B 3.3.2 Table 47 ³¹	

EAG comment: The EAG considers the population characteristics used in the type 1 SMA model appropriate and representative of type-1 SMA population.

6.3.3.3 Interventions and comparators

Same as the presymptomatic model (see Section 6.3.4.3)

6.3.3.4 *Perspective, time horizon and discounting*

Same as the presymptomatic model (see Section 6.3.2.4)

6.3.3.5 *Treatment effectiveness and extrapolation*

The efficacy results used in the type 1 SMA model were informed by the ENDEAR²⁷ and SHINE³⁵ trials. ENDEAR²⁷ had a follow-up of 13 months, therefore the company used data from SHINE³⁵ to overcome the limitations of short follow-up; ENDEAR²⁷ and SHINE³⁵ combined had a total follow-up of 60 months. Participants in SHINE³⁵ included all participants from ENDEAR²⁷, irrespective of whether they received nusinersen or sham procedure in ENDEAR.

EAG comment: The EAG acknowledges short follow-up data limitations from ENDEAR²⁷ and considers the company's approach of overcoming it by using data from SHINE³⁵ appropriate. However, it should be noted that SHINE³⁵ was a single-arm study and therefore in the absence of an appropriate comparator, the efficacy data for nusinersen could have been overestimated.

6.3.3.6 *Health related quality of life*

Same as the presymptomatic model (see Section 6.3.2.7)

6.3.3.7 *Resource use and costs*

Same as the presymptomatic model (see Section 6.3.2.8)

6.3.3.8 *Adverse events*

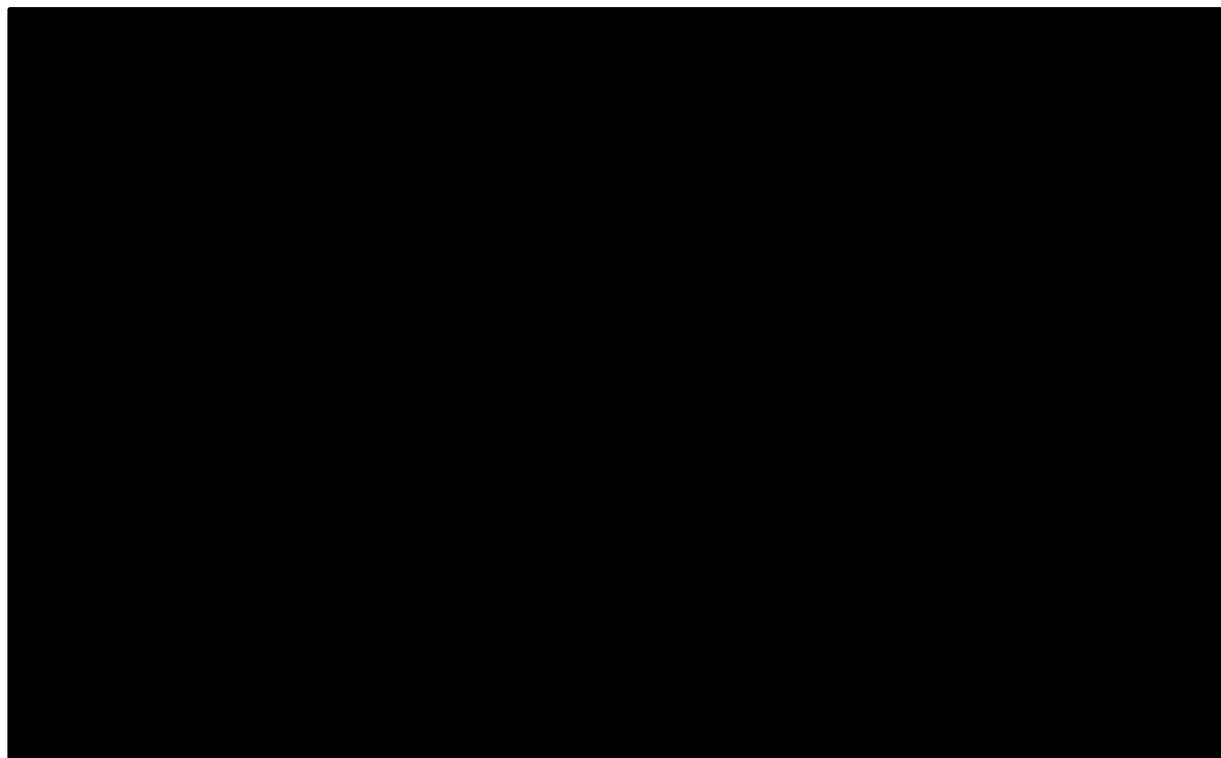
Same as the presymptomatic model (see Section 6.3.2.9)

6.3.3.9 *Survival*

The patient cohort in the type 1 SMA model could transition to 'death' from all the health states in the model. Individual patient level data from ENDEAR²⁷ and SHINE³⁵ was utilised to inform all-cause mortality for the nusinersen treatment cohort in 'permanent ventilation', 'no sitting' and 'sitting without support' health states. Rank preserving structural failure time models (RPSFTM) were used to adjust for treatment switching from ENDEAR²⁷ to SHINE.³⁵ Overall survival for the BSC cohort came from the control arm of ENDEAR.²⁷ Kaplan Meier curves for overall survival were generated and since the proportional hazards assumption was met for all covariables, a joint parametric model was used to extrapolate both arms over the model time horizon. The Weibull parametric curve was selected as it best represented long-term clinical practice (Figure 4). The risk rate was modelled over time and assumed relative hazard rates were constant over time for disease-related mortality, while net hazard rates decreased and then plateaued for both treatments (Figure 5).

The company assumed that there is no increased risk of mortality for the type 1 SMA patient cohort in the 'standing with support' and 'walking independently' health states when compared to the general population. Therefore, the company utilised general population mortality data to inform survival in these two states.

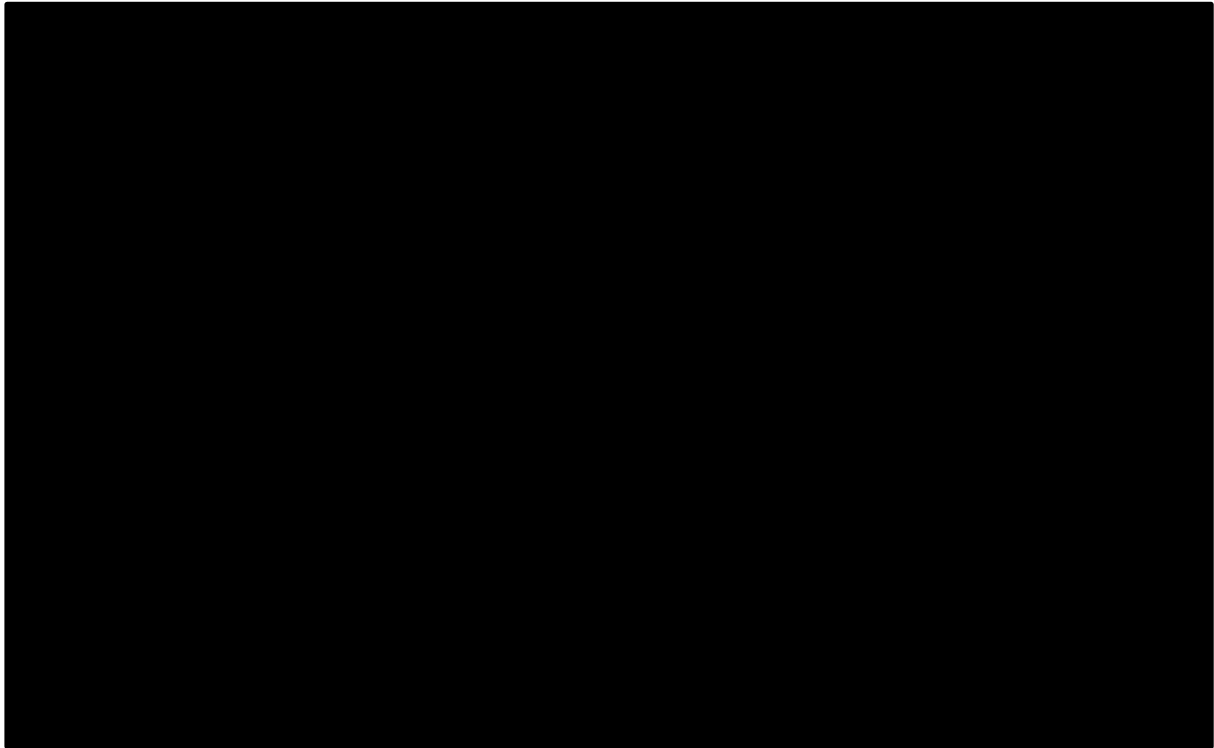
Figure 3: Overall survival in nusinersen and BSC patient cohorts (type 1)



Source: EAG produced from company submitted models

Abbreviations: BSC = best supportive care; OS = overall survival

Figure 4: Comparison of mortality risk between nusinersen and BSC patient cohorts (type 1)

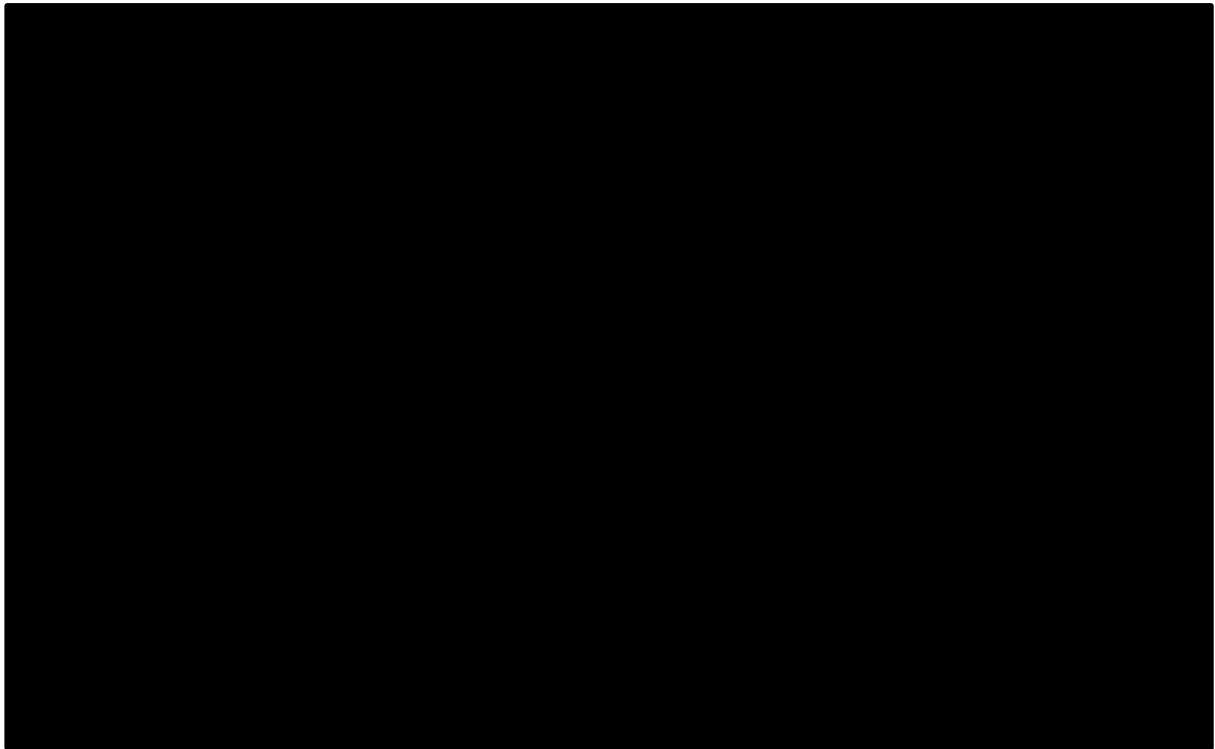


Source: EAG produced from company submitted models

Abbreviations: BSC = best supportive care; OS = overall survival

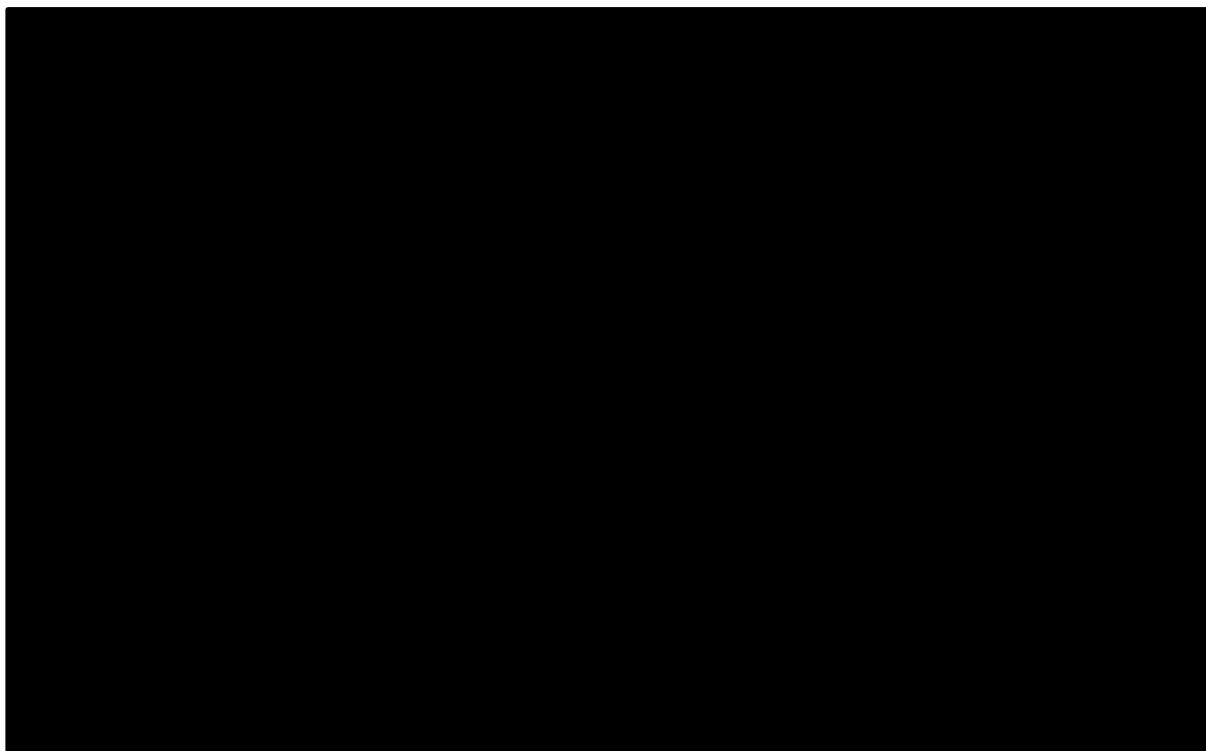
The company's type 1 SMA model assumed that patients could only transition to 'permanent ventilation' from the 'not sitting' health state. The proportion of patients in the nusinersen treatment cohort moving to 'permanent ventilation' was informed by pooled data from ENDEAR²⁷ and SHINE.³⁵ However, the proportion of the BSC cohort moving to 'permanent ventilation' was informed by data from ENDEAR²⁷ alone. Since the proportional hazards assumption was not met, different parametric models were fitted into each Kaplan Meier curve, with a log-normal function for nusinersen and a log-logistic function for BSC considered most plausible by clinical experts. Figure 5 showed an increase in the permanent ventilation hazard for BSC over the first year before decreasing over the subsequent years. Figure 6 showed that the relative risk for nusinersen versus BSC lowered over the first year and became marginally closer over the long term.

Figure 5: Time to permanent ventilation in nusinersen and BSC patient cohorts (type 1)



Source: EAG produced from company submitted models

Abbreviations: BSC = best supportive care; PV: permanent ventilation

Figure 6: Hazard ratio for permanent ventilation (BSC vs nusinersen, type 1)

Source: EAG produced from company submitted models

Abbreviations: BSC = best supportive care; Nus: Nusinersen

EAG comment: The EAG considers the approach taken by the company to estimate the survival data appropriate. Consideration of RPSFTM is expected to improve the internal validity of survival data when treatment switching occurs. The EAG appreciates the use of clinical opinion and goodness-of-fit measures while finding the most plausible parametric curve.

6.3.3.10 Discontinuation

In line with the presymptomatic model (see section 6.3.2.11), the company assumed that any patient who transitions to permanent ventilation would discontinue nusinersen treatment because of their inability to receive the intrathecal administration needed. The company utilised the MAA)¹⁸ data to inform discontinuation in 'not sitting' and 'sitting without support' health states. The MAA)¹⁸ data reported by the company showed that 32 out of 44 patients who discontinued over the 3.5 years switched to OA, where the company reasoned that these patients would have remained in the nusinersen treatment if OA had not become available during the MAA)¹⁸ study and they were not included in the discontinuation data. No patients during the MAA)¹⁸ achieved the ability to stand or walk, and any ability to walk or stand would be considered the result of highly effective treatment. Therefore, the company assumed that when the treatment is considered highly effective, the discontinuation would be low for the health states, 'walking independently' and 'standing with support'. The company assumed a discontinuation rate from nusinersen to BSC of 1.5% per 4-month model cycle for patients 'not sitting' and 'sitting without support' and 1% per-cycle or 'standing with support' and 'walking independently'. After discontinuation, the cohort moved on to receive BSC and incurred costs and outcomes specific to BSC.

EAG comment: The EAG acknowledges the data limitations and considers the company's approach in incorporating discontinuation appropriate. However, it is likely that those discontinuing may not necessarily go on to receive BSC, and instead may go on to receive other disease modifying treatments, when there would be impact on costs and outcomes. Furthermore, the MAA¹⁸ data have short follow-ups which may not be sufficiently long-enough to correctly capture the discontinuations from nusinersen.

6.3.3.11 Disease modifier: severity

Same as presymptomatic model (see Section 6.3.2.12).

6.3.3.12 Company's cost-effectiveness results (type 1)

The company reported both the deterministic and probabilistic results, and the deterministic sensitivity analysis and scenario analyses results. The base-case results are based on the analysis which included carer utilities and considered the PAS discounted price for nusinersen. In the base-case analysis, nusinersen was [REDACTED] over BSC, with an ICER of [REDACTED] (Table 25), which is higher than the NICE's £20,000 willingness to pay threshold. The probabilistic results were generally stable. Nusinersen had a [REDACTED] probability of being cost-effective compared to BSC at a NICE's £30,000/QALY willingness to pay threshold.

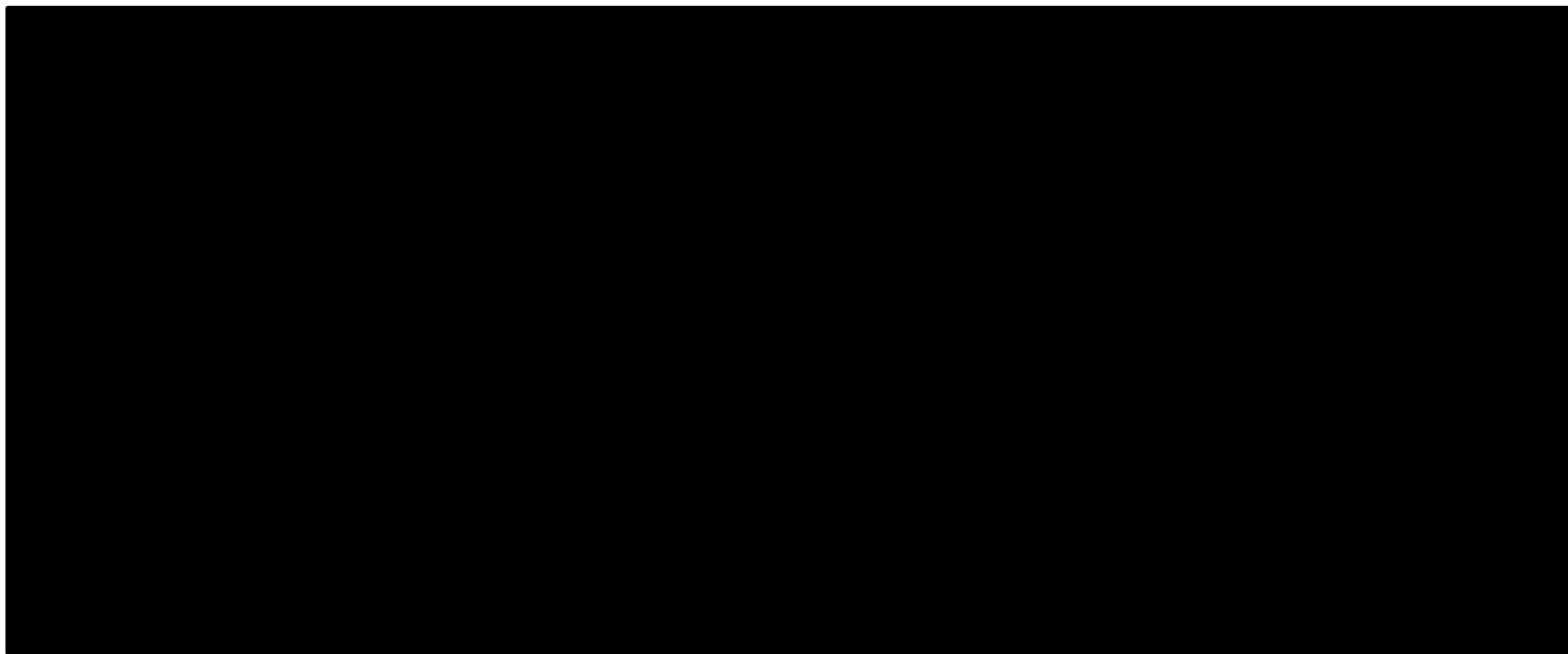
Table 25: Deterministic and probabilistic results for the type 1 SMA population reported by the company (using nusinersen PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB at £30,000 / QALY
Deterministic								
Nusinersen	[REDACTED]	8.38	[REDACTED]	-	-	-	-	-
BSC	[REDACTED]	2.91	[REDACTED]	[REDACTED]	5.47	4.16	[REDACTED]	[REDACTED]
Probabilistic								
Nusinersen	[REDACTED]	8.37	[REDACTED]	-	-	-	-	-
BSC	[REDACTED]	3.05	[REDACTED]	[REDACTED]	5.32	4.09	[REDACTED]	[REDACTED]
Probability cost-effective at £30k willingness to pay								[REDACTED]
Source: originally reported in Biogen CS Section B 3.9.2 Table 79 and Table 80, ³¹ results updated by the company after the points for clarification ³²								
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LYG = life years gained; NHB = net health benefit; QALYs= quality-adjusted life years								

6.3.3.12.1 Deterministic sensitivity analysis (type 1)

One-way sensitivity analysis conducted by the company by varying key input parameters was reported to show that health state utilities had the highest impact on ICER, followed by cost of permanent ventilation and health state costs (Figure 7).

Figure 7: Tornado diagram showing the one-way sensitivity analyses on the type 1 SMA population reported by the company



Abbreviations: BSC = best supportive care; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year

Source: originally reported in Biogen CS Section B 3.10.2 Figure 57,³¹ results updated after the points for clarification³²

6.3.3.12.2 Company's scenario analysis (type 1 SMA)

Assuming utilities from TA588² increased the ICER [REDACTED] to maximum, while removing the background care costs for extended years survived decreased the ICER [REDACTED] below the £20,000/QALY threshold (Table 26).

Table 26: Company's scenario analyses for type 1 SMA population

Scenario	Scenario analysis	ICER
0	Reference	[REDACTED]
1	Alternate utility source: TA588	[REDACTED]
2	Exclude caregiver utility increments	[REDACTED]
3	Exclude active treatment utility increments	[REDACTED]
4	Costs from TA588 (Wickenstones)	[REDACTED]
5	Health state costs for active treatments set to 0 GBP (£) at total discounted BSC LYs	[REDACTED]
6	Assumption that nusinersen cohort does not decline	[REDACTED]
7	The rate of decline for BSC is halved	[REDACTED]
Source: originally reported in Biogen CS Section B 3.10.3 Table 98, ³¹ results updated after the points for clarification ³² Abbreviations: BSC = best supportive care; ICER = incremental cost effectiveness ratio; LY = life years		

EAG comment: The EAG considers the company's presentation of cost-effectiveness results appropriate. The scenario analyses undertaken also are reasonable.

6.3.4 Type 2/3 SMA

6.3.4.1 Model structure

6.3.4.1.1 Type of model:

The company developed a de novo Markov model (

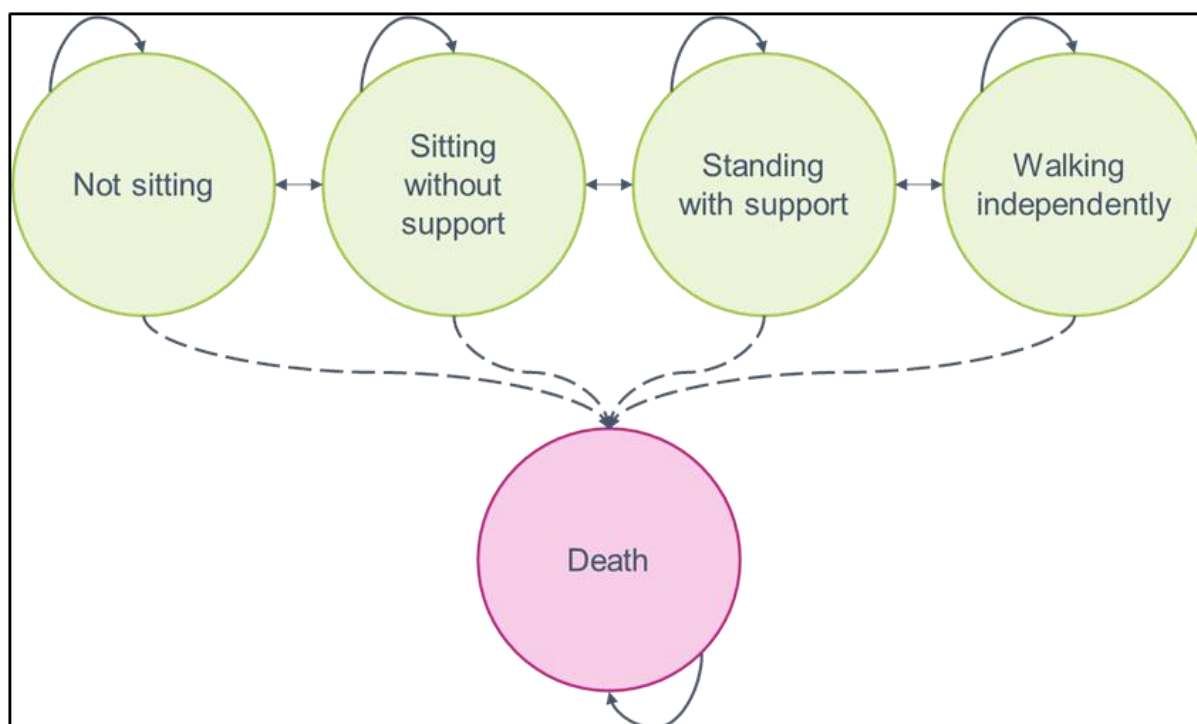
Figure 8) in Microsoft Excel program to assess the cost-effectiveness of nusinersen in type 2/3 SMA population (later onset) primarily informed by TA588.²

6.3.4.1.2 Health states/ events and transitions

The economic evaluation model used to assess the cost-effectiveness of nusinersen in the type 2/3 SMA population had 5 states that captured the gross motor milestones: 'not sitting', 'sitting without support', 'standing with support', 'walking independently', and 'death' as an absorbing state (

Figure 8). The motor milestones were defined using the WHO instrument.³⁷ Unlike the economic models for presymptomatic and type 1 SMA, the economic model for type 2/3 SMA did not include the 'permanent ventilation' state, for which the company provided a justification. The company reported that the decision not to include permanent ventilation aligned with the evidence that permanent ventilation is quite rare in type 2/3 SMA population, and this decision was validated by clinical experts at the advisory board.

Figure 8: Model structure for the later-onset SMA population used by the company (type 2/3)



Source: Biogen CS Section B 3.2.2 Figure 36³¹

EAG comment: The EAG considers the type 2/3 SMA model used by the company appropriate and aligned with the SMA clinical pathway and motor milestones.

6.3.4.2 Population

The model cohort used reflected the baseline characteristics of the ITT population in CHERISH²⁸ and SHINE³⁵ clinical trials for nusinersen. However, both trials consisted of participants predominantly with type 2 SMA, and therefore did not adequately reflect a type 3 SMA population. Therefore, the company utilised information from Wadman et al³⁹ to account for the characteristics of a sub population with type 3 SMA. The company assumed that 100% of the cohort with type 3 SMA were walking at the baseline to reflect the clinical definition of type 3 SMA that all patients with type 3 SMA 'acquire autonomous ambulation' or are walkers. An overall population mean, generated by combining these two populations (type 2 and type 3), informed the economic model. The company reported the type 2, type 3 and combined type 2/3 population characteristics in Table 27.

Table 27: Type 2/3 SMA population characteristics reported by the company

Characteristics	Total later-onset SMA (■)	Type 2 SMA* (■)	Type 3 SMA** (■)
Baseline age (years, mean [SE])	■	■	■
Sex (female, %)	■	■	■
Baseline weight (kg, mean [SE])	■	■	■

Characteristics	Total later-onset SMA (■)	Type 2 SMA* (■)	Type 3 SMA** (■)
Source: Biogen CS Section B 3.3.3 Table 55 ³¹ *Based on the baseline characteristics of all nusinersen and control patients in the CHERISH study ²⁸ **Informed by baseline data from the natural history study reported by Wadman et al ³⁹ Abbreviations: SMA = spinal muscular atrophy; SE = standard error			

EAG comment: The EAG considers the population characteristics used in the type 2/3 SMA model appropriate and representative of type 2/3 SMA population.

6.3.4.3 Interventions and comparators

Same as presymptomatic model (see Section 6.3.2.3)

6.3.4.4 Perspective, time horizon and discounting

Same as presymptomatic model (see Section 6.3.2.4)

6.3.4.5 Treatment effectiveness and extrapolation

The nusinersen effectiveness data used in the type 2/3 SMA economic model primarily came from the CHERISH²⁸ and SHINE³⁵ trials. CHERISH²⁸ was a 15-month multinational trial comparing treatment with nusinersen compared to a sham procedure as a control. To overcome limitations due to the short duration of CHERISH²⁸, the participants from CHERISH²⁸ were enrolled in the SHINE³⁵ trial and were categorised (as previous nusinersen or sham) according to the treatment they received in CHERISH²⁸. The WHO MM data, informed by patient level data from CHERISH²⁸ and SHINE³⁵ over the first 96 months, were directly used in the economic model as a proportion of the cohort occupying each health state in the model (Table 28).

Table 28: Company-reported WHO motor milestone data from CHERISH and SHINE for nusinersen patients used in the type 2/3 SMA model

Time point	Not Sitting	Sitting without support	Standing with support	Walking independently
Baseline	■	■	■	■
Month 6	■	■	■	■
Month 9	■	■	■	■
Month 12	■	■	■	■
Month 15	■	■	■	■
Month 18	■	■	■	■
Month 24	■	■	■	■
Month 36	■	■	■	■
Month 48	■	■	■	■
Month 60	■	■	■	■
Month 72	■	■	■	■
Month 84	■	■	■	■
Month 96	■	■	■	■

Time point	Not Sitting	Sitting without support	Standing with support	Walking independently
Source: Biogen CS Section B 3.3.3 Table 56 ³¹ *Includes patients who were reported as walking independently but were reallocated to meet the definition for type 2 SMA.				

The company assumed all type 2 sub-populations ‘walking independently’ by the end of the trial follow-up in CHERISH²⁸ and SHINE³⁵ trials to be ‘standing with support’ and they were allocated in the economic model accordingly for both nusinersen and BSC arms. It was reported that this assumption is based on the standard definition of SMA where patients following natural history should not be able to walk. The reason behind making the similar assumption for both the model arms was to avoid biasing the model in favour of nusinersen. The company assumed that all type 3 sub-populations “walking independently” at baseline maintained the ability to walk over the first 96 months of the economic model time horizon. This assumption was supported by Wadman et al³⁹, where the ability to walk was sustained until the mean age of 11 years and 34 years for type 3A and 3B populations respectively. As stated earlier, the economic model for type 2/3 SMA used data from combined type 2 and 3 populations.

The company did not have long-term data beyond the 96 months follow-up for nusinersen on the ability of type 2/3 patients to walk, therefore assumption was made for the model cohort to decline by a maximum of one milestone per cycle or by multiple milestones over their lifetime. It was reported that the assumption adhered to what clinical experts observe in clinical practice. The probability of decline for each state was estimated relative to the BSC data reported by Wadman et al³⁹ (Table 29). The inverse of relative risk of improvement (■■■■; corrected estimate after points for clarifications from the EAG), derived using the 15-month follow-up data from CHERISH²⁸ trial on proportions who gained at least one WHO motor milestones each trial arm, were applied to the long-term probabilities of decline in the BSC to derive the probability of decline for nusinersen. These probabilities were assumed equal across all populations and applied for all model cycles 8 years onwards (to reflect the time point at which the trial data ends).

Table 29: Per-cycle probability of decline for nusinersen applied in the company type 2/3 SMA model cycles 8 years onwards

Health state	Per cycle probability of decline (%)		
	Total later-onset SMA	Type 2 SMA	Type 3 SMA
Sitting without support to not sitting	■■■■	■■■■	■■■■
Standing with support to sitting without support	■■■■	■■■■	■■■■
Walking independently to standing with support	■■■■	■■■■	■■■■
Source: originally reported in Biogen CS Section B 3.3.3 Table 57, ³¹ corrected after points for clarification ³² Abbreviations: SMA = spinal muscular atrophy			

The company assumed equivalence of outcomes from the sham control arm of CHERISH²⁸ trial and BSC. Therefore, the patient data from the sham arm informed the proportion of patients in each of the model health states over 15 months of the model time horizon (reflective of CHERISH follow-up duration). The long-term probability of decline was derived from Wadman et al. 2018³⁹ (Table 30) and was applied in each model cycle beyond 15 months. Similar to the nusinersen arm, the assumption was made for the model cohort to decline by a maximum of one milestone per cycle or by multiple milestones over their lifetime.

Table 30: WHO motor milestones used in the BSC arm of the company type 2/3 SMA model

Time point	Not Sitting	Sitting without support	Standing with support	Walking independently
Baseline	■	■	■	■
Month 6	■	■	■	■
Month 9	■	■	■	■
Month 12	■	■	■	■
Month 15	■	■	■	■
*Includes patients who were reported as walking independently but were reallocated to meet the definition for type 2 SMA. Source: Biogen CS Section B 3.3.3 Table 58 ³¹ Abbreviations: SMA = spinal muscular atrophy				

Table 31: Per-cycle probability of decline for BSC cohort used in the company type 2/3 SMA model cycles 8 years onwards

Health state	Per cycle probability of decline (%)		
	Total later-onset SMA	Type 2 SMA	Type 3 SMA
Sitting without support to not sitting	■	■	■
Standing with support to sitting without support	■	■	■
Walking independently to standing with support	■	■	■
Source: originally reported in Biogen CS Section B 3.3.3 Table 59 ³¹ corrected after points for clarification ³² Abbreviations: BSC = best supportive care; SMA = spinal muscular atrophy			

EAG comment: The EAG acknowledges data limitations and considers the company's approach appropriate.

6.3.4.6 Health related quality of life

Same as presymptomatic model (see Section 6.3.2.6).

6.3.4.7 Resource use and costs

Same as presymptomatic model (see Section 6.3.2.8).

6.3.4.8 Adverse events

Same as presymptomatic model (see Section 6.3.2.96.3.4.8).

6.3.4.9 Survival

The health state specific survival data from the SHINE³⁵ extension study were considered immature (), therefore for “not sitting” and “sitting without support” the company used data estimated using survival curves from a Dutch natural history conducted by Wijngaarde et al. 2020.³⁶ A gamma distribution was fitted to survival data from type1c SMA patients for “not sitting” and exponential distribution was fitted to survival data from type 2a and type2b SMA patients for “sitting without support” following the approach in HST24.¹⁶ Although HST24¹⁶ focuses on presymptomatic patients, Biogen argued these set of survival estimates reflected the severity of the disease at the “not sitting” and “sitting without support” states. A hazard ratio was applied to these survival data to reflect those with England and Wales setting. Like the presymptomatic and type1 SMA population, the survival data for health states “standing with support” and “walking independently” were assumed to be equivalent to the general population survival. The company reported that long-term survival data were considered appropriate for both the type 2 and type 3 SMA population.

EAG comment: The EAG acknowledges the limitations in the evidence available and considers the approach taken by the company to estimate the survival data appropriate. However, the company does not report the hazard ratio that was applied to derive the survival data reflecting the England and Wales setting. Therefore, the EAG could not comment on the appropriateness of the hazard ratio applied.

6.3.4.10 Discontinuation

Discontinuation probability data for the type 2/3 SMA were informed by the MAA data over a 3.5 period and were converted to a 4-month probability aligning with the model cycle length (Table 32). As no discontinuation data was available for patients who could stand, the company applied the discontinuation rate for “walking independently” to “standing with support”. The company assumed that these probabilities remained constant over the model time horizon and were considered equivalent for both the type 2 and type 3 sub-populations. After discontinuation, the cohort moved on to receive BSC and incurred costs and outcomes specific to BSC.

Table 32: Per-cycle probability of discontinuation used in company model for type 2/3 SMA

Treatment discontinuation / loss of response	Total population
Per-cycle discontinuation in not sitting (%)	3.2%
Per-cycle discontinuation in sitting without support (%)	3.1%
Per-cycle discontinuation in standing with support (%)	1.0%
Per-cycle discontinuation in walking independently (%)	1.0%
Source: Biogen CS Section B 3.3.3 Table 60 ³¹	

EAG comment: The EAG considers the company's approach to treatment discontinuation to be appropriate. However, it is likely that patients who discontinue may not necessarily transition to BSC alone, but instead some may receive alternative disease modifying treatments, which could have implications for both costs and health outcomes.

6.3.4.11 Decision modifier: Severity

Same as presymptomatic model (see Section 6.3.2.12)

6.3.4.12 Companies' cost-effectiveness results (type 2 and 3 SMA)

The company reported both the deterministic and probabilistic results, and the deterministic sensitivity analysis and scenario analyses results. The base-case results are based on the analysis which included carer utilities and considered the PAS discounted price for nusinersen. In the base-case analysis (based on the executable model received after corrections to relative risk in the points for clarification³²), nusinersen was [REDACTED] over BSC with an ICER of [REDACTED] (Table 33) which was higher than the NICE £20,000 willingness to pay threshold. The probabilistic results were generally stable. Nusinersen had a [REDACTED] probability of being cost-effective compared to BSC at NICE's £30,000/QALY willingness to pay threshold.

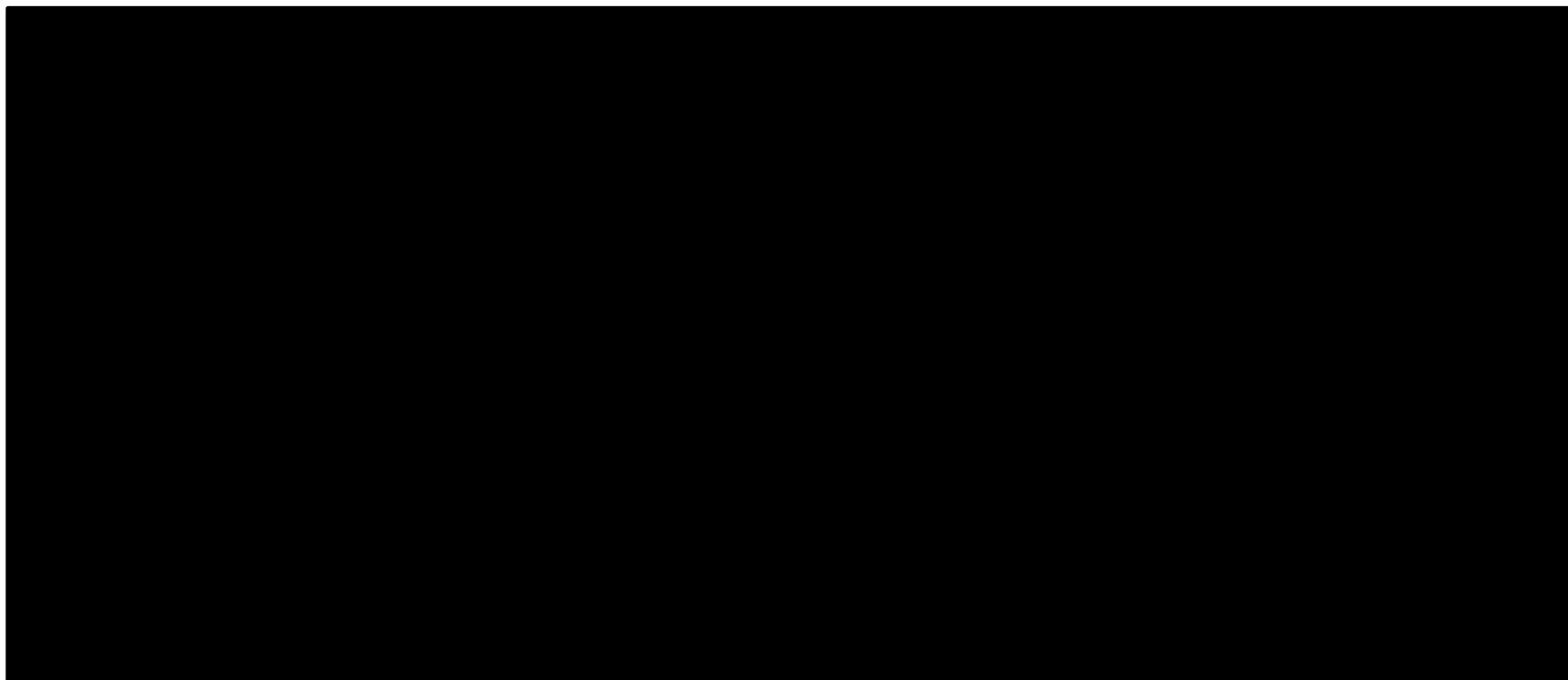
Table 33: Deterministic and probabilistic results for type 2/3 SMA population reported by the company (using nusinersen PAS price)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB at £30,000 / QALY
Deterministic								
Nusinersen	[REDACTED]	23.17	[REDACTED]	=	-	-	=	=
BSC	[REDACTED]	22.86	[REDACTED]	[REDACTED]	0.31	3.95	[REDACTED]	[REDACTED]
Probabilistic								
Nusinersen	[REDACTED]	23.19	[REDACTED]	=	-	-	=	=
BSC	[REDACTED]	22.86	[REDACTED]	[REDACTED]	0.33	3.83	[REDACTED]	[REDACTED]
<i>Probability cost-effective at £30k willingness to pay</i>								[REDACTED]
Source: originally reported in Biogen CS Section B 3.9.3 Table 86 and Table 87, ³¹ corrected after points for clarification ³²								
Abbreviations: BSC = best supportive care; ICER – incremental cost effectiveness ratio; NHB = Net Health Benefits; LYG = life-years gained; QALYs = quality adjusted life year								

6.3.4.12.1 Deterministic sensitivity analysis (Type 2 and 3 SMA)

The parameters with the biggest impact on ICERs were variation in health-state utilities, health-state costs per cycle, treatment-related increases in utility, and discontinuation rates (Figure 9).

Figure 9: Tornado diagram showing the one-way sensitivity analyses on type 2/3 SMA population reported by the company



Source: originally reported in Biogen CS Section B 3.10.2 Figure 58,³¹ results updated after the points for clarification³²

Abbreviations: BSC = best supportive care; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year

6.3.4.12.2 Companies' scenario analysis (type 2 and 3 SMA)

Scenarios with the largest impact on cost-effectiveness were assuming no long-term decline with nusinersen and assuming no treatment-related utility increments. However, the drop in ICER should be noted when alternative source of utility was used.

Table 34: Company's scenario analyses for type 2/3 SMA population

Scenario	Scenario analysis	ICER
0	Reference	
1	The rate of decline for BSC is halved	
2	Remove carer utility increments	
3	Remove active treatment increments	
4	Assumption that nusinersen cohort does not decline	
5	Alternate utility source: TA588	
6	Costs from TA588	
7	Type 2 sub-population standing with support and walking independently as per CHERISH / SHINE	
Source: originally reported in Biogen CS Section B 3.10.3 Table 99 ³¹ , results updated after the points for clarification ³² Abbreviations: BSC = best supportive care; ICER = incremental cost effectiveness ratio;		

EAG comment: The EAG considers the company's presentation of cost-effectiveness results to be appropriate and the scenario analyses undertaken are also reasonable. However, it should be noted that uncertainty in the utility data could significantly impact the ICER, with any changes in these data potentially leading to substantial variations in the results.

6.3.5 Model validation and face validity check

The company reported that a technical validity check was conducted for all the three models where the checks primarily ensured the formulae used in the models were correct and appropriately applied. A quality assurance checklist was utilised and covered a range of tests including sense checks such as changing certain inputs to zero and confirming the effect was as expected. The technical validity check was conducted by a health economist not directly involved in the model development.

In addition, face validity of the models was examined during UK advisory board by describing the model structure and inputs to UK clinical experts and health economists to ensure the model approach appropriately captured the costs and outcomes in UK clinical practice. The company reported that there were some specific changes after the advice from the advisory board.

EAG comment: The EAG identified some errors in the calculations of relative risks used in the models, which was subsequently corrected by the company following the EAG's points for clarifications.³² In addition, there were some minor errors (e.g. omission of the total additional utility gains from treatment in the total undiscounted QALYs). However, these issues did not change the conclusions. The VBA codes used in the model appeared appropriate.

7 Critique of Roche submission

7.1 Critique of Roche decision problem

Roche stated that their decision problem was “as per NICE final scope and in line with NICE reference case” in relation to all elements (population, intervention, comparator and outcomes). However, there were some differences between eligibility criteria of the Roche SLR from the NICE decision problem.

7.1.1 Population

The eligible population included people with type 1 or type 2/3 SMA and did not include people with type 0 or type 4 SMA, who were included in the NICE decision problem. These exclusions mean that there is no cost-effectiveness evidence surrounding risdiplam for these populations and conclusions about cost-effectiveness therefore cannot be drawn for these subgroups.

7.1.2 Intervention

In addition to risdiplam and nusinersen, the company included reldesemtiv, apitegromab, RO7204239 and branaplam as interventions, although they noted that this was outside of scope for this submission. Although a discrepancy compared with the NICE decision problem, this would not have led to missing data and is not considered an area of concern by the EAG.

7.1.3 Comparators

The company specified comparators as comparing the interventions of interest to each other, or to placebo or standard of care.

7.1.4 Outcomes

The company included all outcomes from the NICE decision problem, except for stamina and fatigue. It should be noted that that stamina and fatigue are outcomes considered important by professional and patient organisations in discussion with the EAG.

Table 35: Roche decision problem, reproduced from document B table 1

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with 5q spinal muscular atrophy	As per NICE final scope and in line with NICE reference case	N/A
Intervention	Risdiplam	As per NICE final scope and in line with NICE reference case	N/A
Comparator(s)	- Established clinical management - The interventions will be compared to each other In addition, for children aged 12 months and under with a bi-allelic mutation in the <i>SMN1</i> gene and present with a clinical diagnosis of type 1 SMA or presymptotically with up to 3 copies of the <i>SMN2</i> gene - Onasemnogene abeparvovec - Nusinersen - Best Supportive Care (BSC)	As per NICE final scope and in line with NICE reference case	N/A
Outcomes	The outcome measures to be considered include: - Motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills) - Bulbar function (including, for example, swallowing and ability to communicate) - Frequency and duration of hospitalisation	As per NICE final scope and in line with NICE reference case	N/A

	• Respiratory function • Complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation • Stamina and fatigue • Mortality • Adverse effects of treatment • Health-related quality of life		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.	In the presymptomatic population, a cost-comparison has been used to compare risdiplam to nusinersen and onasemnogene abeparvovec	Given insufficient comparative efficacy data, equal efficacy had to be assumed

Subgroups to be considered	If the evidence allows the following subgroups will be considered: • SMA type • Number of <i>SMN2</i> gene copies • Functional status (non-sitter, sitter, walker) • People who have had prior active treatment for SMA	As per NICE final scope and in line with NICE reference case	N/A
Special considerations including issues related to equity or equality	In the current funding situation, the MAA for risdiplam excludes patients who are permanently ventilated or have a tracheostomy. The situation has developed significant in the past few years, and clinicians now report an improvement in quality of life or a slowing of the expected deterioration in motor / respiratory function.	Permanently ventilated patients have been presented as a subgroup to consider (B.2.7.5)	In the current situation, the decision to treat permanently ventilated patients must be taken to an NHSE panel, delaying treatment and potentially worsening prognosis
Abbreviations: MAA = managed access agreement; NICE = National Institute for Health and Care Excellence; SMN1 = survival motor neuron 1 ; SMN2 = survival motor neuron 2;			

7.2 Critique of Roche SLR

7.2.1 Search strategies

The company conducted the original search in January 2018, and updated this search in January 2020, and again in June 2021, and finally in February 2023. A range of electronic bibliographic databases were searched, and the company report study design limitations but did not report the use of design filters. Conference abstracts were sought on multiple databases covering year to year inclusive. The company stated that English language limitations were imposed on the searches.

The search strategy has not been provided by the company and, whilst the PICO is provided, there is no reporting of the concepts used in the search.

The EAG were unable to appraise the searches using the PRESS checklist and the latest NICE methods manual.^{21,22} The number of records retrieved per search line was not shown and the methods and terms used to search the conference abstracts were not presented as might be expected when using the PRISMA-S reporting guidance.²³ It was therefore impossible to judge whether the evidence presented in the company's SLR was complete.

7.2.2 Inclusion and exclusion criteria

Table 36 presents the inclusion and exclusion criteria for the Roche SLR.

Table 36: Inclusion and exclusion criteria for Roche SLR, reproduced from Appendix D table 3

Domain	Details
Population	• Indication: SMA (Presymptomatic: Type 1, Type 2, and Type 3) • Age groups: Paediatric and adult • Ethnicity: no restrictions
Intervention	Studies assessing the following pharmacological interventions in SMA were included: • Risdiplam (Evrysdi) • Nusinersen (Spinraza) • Onasemnogene abeparvovec (Zolgensma) • Reldesemtiv (CK-107) • Apitegromab (SRK-015) • RO7204239 • Branaplam (LMI070)
Comparator	• Studies comparing interventions of interest (as monotherapy or combination therapy) either to each other or to placebo or standard of care were included • Studies assessing interventions of interest without any comparator group (single-arm studies) were also included

Domain	Details
Outcomes*	- Efficacy: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND); Bayley Scales of Infant and Toddler Development-Third Edition (Bayley-III); Hammersmith Infant Neurological Examination-Section 2 (HINE-2); Hammersmith Functional Motor Scale (HFMS); Hammersmith Functional Motor Scale-Expanded (HFMSE); Motor Function Measure-32 (MFM-32); achievement of motor milestones; WHO motor milestones; survival rates; event-free survival (time to death/ use of permanent ventilation); ventilator use; Upper Limb Module (ULM); Revised Upper Limb Module (RULM); 6-Minute Walk Test (6-MWT); compound muscle action potential (CMAP) amplitude; respiratory outcomes; scoliosis; hospitalisation; bulbar function - HRQoL: Paediatric Quality of Life Inventory (PedsQL) - Safety: Adverse events (AEs), discontinuations
Study design	Inclusion criteria - RCTs - Non-RCTs - Single-arm trials - Real-world observational studies (prospective and retrospective) Exclusion criteria - Cross-sectional studies - Case series / case reports Previously published systematic reviews and meta-analyses were included for bibliographic searches to identify relevant primary studies.
Language	English language only
Country	No restriction
Search timeframe	- Original SLR (2018): Database inception- 31st January 2018 - First update (2020): 1st February 2018- 22nd January 2020 - Second update (2021): 1st January 2020- 8th June 2021 - Third update (2023): 1st June 2021- 16th February 2023
Abbreviations: RCT = randomised controlled trial; SLR = systematic literature review	

The eligible population included people with type 1 or type 2/3 SMA and did not include people with type 0 or type 4 SMA. In addition to risdiplam and nusinersen, the company included reldesemtiv, apitegromab, RO7204239 and Branaplam as interventions. Although they noted that this was outside of scope for this submission, this would not have led to missing data. The company specified comparators as comparing the interventions of interest to each other or to placebo or standard of care. Eligible outcomes included motor function, paediatric quality of life, adverse events and discontinuations (see Table 36 for details).

7.2.3 SLR methods

Table 37: EAG evaluation of Roche SLR

Systematic review stage	Section in CS where methods are reported	EAG's assessment of the robustness of methods
Data sources	Appendix D Section D1	Appropriate Multidisciplinary electronic databases searched and described in full. The company have searched relevant SMA conferences. The company have searched for ongoing/unpublished studies in a range of databases.
Search strategies	Not reported	Key concern Due to non-reporting of the search strategy, it is impossible to know if relevant search terms used and combined appropriately. Furthermore, it is impossible to know if the searches excluded (NOT) terms. English language limitations have been applied without justification.
Search filters	Not reported	Key concern Due to non-reporting of the search strategy it is impossible to know if design were filters used, and if so whether this was done appropriately.
Eligibility criteria	Appendix D, D.1 table 3	Some concerns The population included people with presymptomatic SMA and SMA types 1, 2, and 3 but did not include people with types 0 and 4. Interventions included drugs not mentioned in the NICE decision problem as well as risdiplam, nusinersen and OA (although they were noted by the company as out of scope for this appraisal and would not lead to missing relevant evidence in the SLR). The company did not include stamina or fatigue in their pre-specified outcomes. They included RCTs, non-RCTs and single-arm studies. They excluded case studies and case reports and did not report any specific limitations on number of patients in a study.
Screening	Appendix D, D.1	Appropriate Both titles and abstract and full text screening were each conducted by two people independently, with disagreements adjudicated by a reviewer.
Data extraction	NR	Some concerns No information is given about the data extraction process for the SLR, although there is a note in the legend of table 3 indicating 'a comprehensive list of ~40 outcomes from the data extraction sheet'. It could be assumed that the data extraction process was similar to that described for the economic SLR where one reviewer extracted data and a second reviewer independently checked it.

Quality appraisal	NR	Some concerns No information is given about the methods for appraising the quality of the included studies, although from Table 4 in Appendix D it appears that they used the Cochrane Risk of Bias tool for RCTs. There appears to be no quality appraisal presented for other study designs.
Data synthesis	Document B sections B.2.9.2	Some concerns/key issue Since no trials were found comparing risdiplam to nusinersen or OA, the company conducted a feasibility assessment for an indirect comparison between the drugs. They conducted a naïve comparison for the presymptomatic population, MAICs for type 1 patients, and an anchored MAIC for type 2/3 patients (Section 7.2.4).
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; MAIC = matching-adjusted indirect comparison; OA = Onasemnogene abeparvovec; SLR = systematic literature review		

7.2.4 Critique of Roche ITC

Roche utilised naïve treatment comparisons for presymptomatic patients, unanchored MAICs and STCs for type 1 patients, unanchored and anchored MAICs in type 2/3 patients. For the selection of covariates, Roche utilised information from multiple sources, including a prognostic review, other published literature and clinical opinion. Explanations of what covariates were included per comparison for each group of SMA patients are tabulated (tables 54-56 in Roche document B) with justification for include or exclude designation.⁴⁴

Eighteen analyses were conducted by Roche (12 comparing to nusinersen and six comparing to OA). A MAIC or STC assessment of presymptomatic patients was deemed not feasible. This was due to the low numbers and differences between key variables (e.g. number of SMN2 copies). To allow for this comparison, Roche synchronised the timing of outcomes, using a schedule matching method.⁴⁵ The naïve comparisons in this group were conducted using t-test analyses. The company state that these analyses were purely exploratory and only conducted on the absolute mean value at each time point. The analyses therefore do not take into account any differences between the studies. No statistically significant differences were found between nusinersen or OA and risdiplam for CHOP-INTEND, HINE-2, or BSID-III motor milestones (inclusive of sitting without support, standing alone, standing with assistance, and walking unaided).

In type 1 patients, when comparing risdiplam to OA, an STC was the preferred analysis, although the company submission does report the results for both the STC and unanchored MAICs. STC was preferred due to the reduction in ESS, which was <5 compared to STR1VE-US and <20 compared to STR1VE-EU (see Table 38). The EAG agree with this preference, however, as the results are derived from an STC, there may be inherent biases. For example, when data is non-linear, which can commonly be the case in SMA where it is possible to show improvements, maintenance or deterioration over time, results can be open to bias.²⁵ Specifically, as the results are generated via a linear regression model using IPD from one trial (in this case, risdiplam) compared to aggregate data from the comparator trial (in this case, OA) the non-linearity assumption may be violated. If there is non-linearity, substituting the mean covariate values from the comparator trial into the regression can lead to biased

estimates, due to issues between the relationship of the mean of the outcome and the mean of the covariates.²⁶ Therefore, it is important to consider the results with caution. For risdiplam compared to nusinersen, unanchored MAICs suggested a statistically significant difference between the treatments for CHOP-INTEND, HINE-2, adverse events and survival (see Table). The ESS for these analyses is >35, which suggest the potential for less bias and uncertainty in these results.⁴⁶

In type 2/3 patients, when comparing risdiplam to nusinersen, an anchored MAIC was utilised when assessing up to 12 months. An unanchored MAIC was utilised for assessing beyond 12 months, as the placebo and sham groups from the studies began treatment and therefore there was no comparator. To conduct the anchored MAICs, the company assumed the placebo and sham arms of the trials were the same. However, the placebo (oral, as the intervention) and sham (small needle prick to simulate the intervention) may not be comparable due to the difference in modality. Furthermore, the ESS for the placebo arm in risdiplam for this comparison was <10 and the intervention arm was <30 (see Table 38). The company highlights this as a limitation and mentions the increase in uncertainty of the relative effects. This is in line with NICE TSD 18,²⁴ which states that a small ESS suggests a potential for high variability between the populations being compared, meaning the estimate may be unstable. It is therefore recommended to treat the results of the anchored MAIC with caution. Additionally, the company highlight that when using the comparator arms for matching, these arms become the assumed target population (rather than the intended intervention arms). This presents an issue for type 2/3 patient comparisons due to the differences in eligibility criteria, as most SUNFISH (risdiplam) patients would not have been enrolled in CHERISH (nusinersen). The company also mentioned attempts to increase ESS for the anchored MAIC, via stepwise exclusion of covariates (i.e. SMN2 copies and baseline score). However, the reduction in ESS was mainly driven by age, and removal of other factors had minimal impact on ESS. The anchored MAICs suggested no statistically significant differences between risdiplam and nusinersen. The one unanchored MAIC for RULM (baseline change to 12, 24 and 36 months) also suggested no statistically significant differences between the two treatments.

Overall, clear attempts were made to make the analyses possible and plausible with the data available to the company for statistical assessments. Concerns about sample sizes and naïve analysis are warranted. However, this is mainly driven by availability of data in a rare disease. The anchored MAIC in type 2/3 was conducted using the data available. However, it does raise concerns in terms of the comparability of the placebo and sham arms of the trials. Additionally, the reduced ESS in both the intervention and control arms suggest a lack of comparability between the two cohorts. Table provides an overview of the results from the Roche company submission.

Table 38: Overview of the results from the Roche company submission

Outcome	Population	Analysis Type	Comparator	Covariates	Sample size/ ESS	Conclusion
CHOP-INTEND	Presymptomatic	Naïve comparison	Nusinersen (NURTURE)	SMN2 copy number, mean age at first dose, mean baseline total CHOP INTEND score	RAINBOWFISH: 13 NURTURE: 15 Note: ESS not applicable	RAINBOWFISH vs NURTURE suggests no statistically significant differences.
HINE-2	Presymptomatic	Naïve comparison	Nusinersen (NURTURE)	SMN2 copy number, mean age at first dose, mean baseline total CHOP INTEND score	RAINBOWFISH: 13 NURTURE: 15 Note: ESS not applicable	RAINBOWFISH vs NURTURE suggests no statistically significant differences.
BSID-III motor milestones	Presymptomatic	Naïve comparison	Nusinersen (NURTURE)	SMN2 copy number, mean age at first dose, mean baseline total CHOP INTEND score	RAINBOWFISH: 13 NURTURE: 15 Note: ESS not applicable	RAINBOWFISH vs NURTURE demonstrated no statistically significant differences for sitting without support, standing alone, standing with assistance, and walking unaided.
BSID-III motor milestones	Presymptomatic	Naïve comparison	OA (SPR1NT)	SMN2 copy number, mean age at first dose, mean baseline total CHOP INTEND score	RAINBOWFISH: 13	RAINBOWFISH vs SPR1NT suggest no statistically significant differences.

Outcome	Population	Analysis Type	Comparator	Covariates	Sample size/ ESS	Conclusion
					SPR1NT: 10 Note: ESS not applicable	
CHOP-INTEND	Type 1	Unanchored MAIC	Nusinersen (ENDEAR-SHINE)	Mean age at first dose, mean baseline total CHOP INTEND score, mean disease duration at baseline	FIREFISH: 58/40.6	FIREFISH vs ENDEAR-SHINE suggested statistically significant difference in obtaining improvement (≥ 4 points) in favour of risdiplam.
HINE-2	Type 1	Unanchored MAIC	Nusinersen (ENDEAR-SHINE)	Mean age at first dose, mean baseline total CHOP INTEND score, mean disease duration at baseline	FIREFISH: 58/40.6	FIREFISH vs ENDEAR suggested statistically significant difference in motor milestone response in favour of risdiplam.
Adverse events	Type 1	Unanchored MAIC	Nusinersen (ENDEAR-SHINE)	Mean age at first dose, mean baseline total CHOP INTEND score, mean disease duration at baseline	FIREFISH: 58/40.6	FIREFISH vs ENDEAR-SHINE suggested statistically less adverse events in favour of risdiplam.
Event free survival	Type 1	Unanchored MAIC	Nusinersen (ENDEAR-SHINE)	Mean age at first dose, mean baseline total CHOP INTEND score, mean disease duration at baseline	FIREFISH: 58/40.6	FIREFISH vs ENDEAR-SHINE suggested statistically significant increase in event free survival in favour of risdiplam.

Outcome	Population	Analysis Type	Comparator	Covariates	Sample size/ ESS	Conclusion
Overall survival	Type 1	Unanchored MAIC	Nusinersen (ENDEAR-SHINE)	Mean age at first dose, mean baseline total CHOP INTEND score, mean disease duration at baseline	FIREFISH: 58/40.6	FIREFISH vs ENDEAR-SHINE suggested statistically significant increase in survival in favour of risdiplam.
CHOP-INTEND	Type 1	STC (preferred) Unanchored MAIC	OA (STR1VE)	Mean age at first dose, mean baseline total CHOP INTEND score	FIREFISH vs STR1VE-US: 58/2.1 FIREFISH vs STR1VE-EU: 62/15.32	FIREFISH vs STR1VE suggested no statistically significant differences, with wide 95% confidence intervals for odds ratios.
Adverse events	Type 1	STC (preferred) Unanchored MAIC	OA (STR1VE)	Mean age at first dose, mean baseline total CHOP INTEND score	FIREFISH vs STR1VE-US: 58/2.1 FIREFISH vs STR1VE-EU: 62/15.32	FIREFISH vs STR1VE suggested no statistically significant differences.
BSID-III motor milestones	Type 1	STC (preferred) Unanchored MAIC	OA (STR1VE)	Mean age at first dose, mean baseline total CHOP INTEND score	FIREFISH vs STR1VE-US: 58/2.1 FIREFISH vs STR1VE-EU: 62/15.32	FIREFISH vs STR1VE suggested no statistically significant differences.

Outcome	Population	Analysis Type	Comparator	Covariates	Sample size/ ESS	Conclusion
Event free survival	Type 1	STC (preferred) Unanchored MAIC	OA (STR1VE)	Mean age at first dose, mean baseline total CHOP INTEND score	FIREFISH vs STR1VE-US: 58/2.1 FIREFISH vs STR1VE-EU: 62/15.32	FIREFISH vs STR1VE suggested no statistically significant differences.
Ventilation free survival	Type 1	STC (preferred) Unanchored MAIC	OA (STR1VE)	Mean age at first dose, mean baseline total CHOP INTEND score	FIREFISH vs STR1VE-US: 58/2.1 FIREFISH vs STR1VE-EU: 62/15.32	FIREFISH vs STR1VE suggested no statistically significant differences.
RULM change from baseline to 12 months	Type 2/3	Anchored MAIC	Nusinersen (CHERISH)	Mean age at screening, mean RULM baseline score, and mean SMN2 copy number	SUNFISH risdiplam: 43/28.3 SUNFISH placebo: 25/8.8	SUNFISH vs CHERISH suggested no statistically significant differences and wide 95% confidence intervals.
RULM change from baseline to 12, 24, and 36 months	Type 2/3	Unanchored MAIC	Nusinersen (CHERISH)	Mean age at screening, mean RULM baseline score,	SUNFISH: 43/29.8	SUNFISH vs CHERISH suggested no statistically significant differences at each timepoint.

Outcome	Population	Analysis Type	Comparator	Covariates	Sample size/ ESS	Conclusion
				and mean SMN2 copy number		
HFMSE	Type 2/3	Anchored MAIC	Nusinersen (CHERISH)	Mean age at screening, mean RULM baseline score, and mean SMN2 copy number (note: analyses not presented but assumed to be same as previous)	SUNFISH risdiplam: 43/28.3 SUNFISH placebo: 25/8.8	SUNFISH vs CHERISH analysis observed differences in response for placebo of SUNFISH to natural history and sham of CHERISH. MAIC results not reported.
Adverse events	Type 2/3	Anchored MAIC	Nusinersen (CHERISH)	Mean age at screening, mean RULM baseline score, and mean SMN2 copy number	SUNFISH risdiplam: 43/28.3 SUNFISH placebo: 25/8.8	SUNFISH vs CHERISH suggested no statistically significant differences and wide 95% confidence intervals.
Abbreviations: BSID-III = Bayley Scales of Infant and Toddler Development, Third Edition; CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; ESS = Effective sample size; HFMSE = Hammersmith Functional Motor Scale (expanded); HINE-2 = Hammersmith Infant Neurological Examination - Part 2; MAIC = matching-adjusted indirect comparison; OA = onasemnogene abeparvovec; RULM = Revised Upper Limb Module; STC = Simulated Treatment Comparison						

7.2.5 Critique of Roche MAA

7.2.5.1 Paediatric registry

The paediatric registry updated the following items in April 2025.

- WHO MM information
- Updated descriptive data for HINE-2 in SMA type 1,
- Mortality
- Number of patients with permanent ventilation
- EK-2 overview

Data for WHO MM was provided over time, with number of patients per SMA type, who WAS in each classification (e.g. non-sitters, sitting without support, crawling).

In the original report, MMRMs were conducted for the following outcomes and SMA types.

- RHS: type 2/3
- RULM: type 2/3

MMRM models include the following covariates.

- Age at symptom onset
- Age at treatment initiation
- Time between diagnosis and treatment initiation
- Baseline motor function milestone categorised by walkers/sitters or non-sitters (for SMA Type 2/3 model only)
- Weight

No statistical analysis was undertaken for the following motor outcomes:

- CHOP-INTEND: type 1
- RHS: type 1
- RULM: type 1
- HINE: type 1

Modelling was deemed infeasible due to low patient numbers, instead descriptive data is reported.

Over the original and updated reports, MMRM were conducted when feasible (i.e. there was enough data). In cases of insufficient data, results are generally reported narratively and tabulated (e.g. means and SDs). Not all outcomes provided are mandated (e.g. EK-2) but are still provided, with the caveat that data cleaning was not as thorough for MAA mandated items.

Overall, the EAG considers that analyses of the data are conducted when plausible and the limitations of the data are clearly highlighted within the report.

7.2.5.2 Adult registry

The adult registry updated all analyses from the original report (December 2023) therefore the new (April 2025) report is to be considered here. Data was presented for the following:

- WHO MM information
- MMRM for ATEND (left and right)

- MMRM for EK2
- MMRM for RULM
- MMRM for RHS
- MMRM for 6 Minute Walk Test (6MWT)

MMRMs were adjusted for the following baseline covariates.

- Patient (random effect)
- Age at symptom onset (fixed effect)
- Age at treatment initiation (fixed effect)
- SMA type (fixed effect)
- Treatment duration at time of visit (fixed effect)
- Disease duration (age at treatment state minus age at symptom onset; fixed effect)

To increase data availability, the registry removed requirement for at least one follow-up score and weight as a covariate. Removal of the criteria of at least one follow-up score increased both the number of patients and value of data (i.e. scores) contributing to the models. Weight was not used due to a large amount of missing data. The previous report (December 2023) included a sensitivity analysis for patients naïve to treatment and pre-treated patients. Additionally, the updated report (April 2025) split by status (i.e. non-sitters, sitters, and walkers), whereas the previous report (December 2023) assessed type 2/3 patients as a whole. The new report therefore offers more granularity in terms of subgroups of SMA 2/3 patients but does suffer from smaller patient sample sizes. When patient numbers are below five, no results are calculated for that follow-up period.

Overall, the EAG considers that analyses are conducted using appropriate methods and attempts have been made to provide context to the results and consider type 2/3 patients as separately as possible.

7.2.6 Results of Roche SLR

One phase II randomised controlled trial has been conducted for children and young people with type 2 and non-ambulant type 3 SMA, comparing risdiplam with placebo in part 1, and then shifting to an open-label phase in part 2 (SUNFISH) with five year follow-up.⁴⁷⁻⁵³ This is the only controlled trial of risdiplam.

A phase II/III single arm trial has been conducted for infants between 1 and 7 months with type 1 SMA (FIREFISH),⁵⁴⁻⁵⁶ with a primary analysis at month 12 and open-label extension phase of three years. An ongoing phase II single arm trial for presymptomatic genetically diagnosed infants under 6 weeks of age (RAINBOWFISH)⁵⁷⁻⁶⁰ is due to complete in 2027. A phase II single arm trial (JEWELFISH) has recently completed for adult and paediatric patients who have previously received nusinersen, OA or olesoxime (a drug previously in development but terminated).^{61,62}

Finally, the company incorporated real-world data from the adult and paediatric REACH registries into their economic model.

Further characteristics of these studies are shown in Table 39.

Table 39: Overview of clinical effectiveness evidence for risdiplam (reproduced from Roche submission table 5)

Study	BP39056 (FIREFISH)
Study design	Open-label, two-part seamless, multicentre, single-arm study. Part 1 objectives: safety, tolerability, PK and PD, dose selection for Part 2 Part 2 objectives: efficacy, safety and tolerability, PK and PD
Population	Infants with type 1 SMA aged ≥ 1 month and ≤ 7 months at the time of enrolment
Intervention(s)	Risdiplam
Comparator(s)	None (single arm)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale for use/non-use in the model	FIREFISH is a Phase II/III trial providing efficacy and safety evidence for risdiplam in people with type 1 SMA. Data from Part 2 of the study were used to inform the efficacy and safety of risdiplam in the economic model
Reported outcomes specified in the decision problem	Motor function (BSID III, HINE-2, CHOP-INTEND); bulbar function; survival and ventilation-free survival; healthcare utilisation; adverse events, HRQoL
Study	BP39055 (SUNFISH)
Study design	Two-part seamless, randomised, multicentre, placebo-controlled, double-blind study. Part 1 objectives: safety, tolerability, PK and PD, dose selection for Part 2 Part 2 objectives: efficacy, safety and tolerability, PK and PD
Population	People aged 2–25 years with type 2 and non-ambulant type 3 SMA
Intervention(s)	Risdiplam
Comparator(s)	Placebo for the first 12 months Single arm OLE for the remaining 4 years
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale for use/non-use in the model	SUNFISH is a Phase II/III trial providing efficacy and safety evidence for risdiplam in people with type 2 or 3 SMA. Data from Part 2 of the study were used to inform the efficacy and safety of risdiplam in the economic model
Reported outcomes specified in the decision problem	Motor function (MFM32, RULM, HFMSE); adverse events; HRQoL
Study	RAINBOWFISH
Study design	Open-label, single-arm, multicentre study

Population	People aged from birth to 6 weeks (at first dose) who have been genetically diagnosed with SMA (<i>SMN1</i> deletion and any <i>SMN2</i> copies) but not yet presenting with SMA symptoms
Intervention(s)	Risdiplam
Comparator(s)	None (single arm)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale for use/non-use in the model	RAINBOWFISH provides efficacy and safety evidence for risdiplam for presymptomatic patients with a genetic diagnosis of SMA. Data from this study were used to inform the efficacy and safety of risdiplam in the economic model
Reported outcomes specified in the decision problem	Motor function (BSID-III, HINE-2, CHOP-INTEND, survival and ventilation-free survival, nutritional status (ability to swallow and feed orally)
All other reported outcomes	Development of clinically manifested SMA, growth measures (weight, length, height, head circumference, chest circumference), degree of innervation (CMAP amplitude)
Study	BP39054 (JEWELFISH)
Study design	Multicentre, open label, non-comparative, single-arm, exploratory study in SMA patients previously enrolled in BP29420 (MOONFISH) or previously treated with nusinersen, onasemnogene abeparvovec or olesoxime. 24 month treatment period plus extension phase
Population	People aged 6 months to 60 years with type 1, 2 and 3 SMA
Intervention(s)	Risdiplam
Comparator(s)	None (single arm)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	No
Rationale for use/non-use in the model	The primary objective was safety, all efficacy outcomes were exploratory
Reported outcomes specified in the decision problem	Adverse events, motor function (MFM-32, HFMSE, RULM, 6MWT, BSID-III, HINE-2), HRQoL, survival and ventilation-free survival
Study	REACH registries
Study design	Adult and paediatric SMA registry datasets, collecting observational data on the use of risdiplam within the real world setting.
Population	Patients treated with risdiplam under the MAA
Intervention(s)	Risdiplam
Comparator(s)	None (observational study)

Indicate if study supports application for marketing authorisation	No
Indicate if study used in the economic model	The baseline characteristics are included as a scenario analysis.
Rationale if study not used in model	The REACH registries provide real-world efficacy evidence for risdiplam paediatric and adult SMA patients. The observational baseline data from this study were used to inform a scenarios analysis in the economic model. However, the efficacy and safety data was insufficient to be modelled.
Reported outcomes specified in the decision problem	Motor function (CHOP-INTEND, RHS, RULM, HINE, Adult registry; ATEND, EK2), survival and ventilation-free survival
Abbreviations: ATEND = Adapted Test of Neuromuscular Disorders; BSID-III = Bayley Scales of Infant and Toddler Development, Third Edition; CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; ESS = Effective sample size; HFMSE = Hammersmith Functional Motor Scale (expanded); HINE-2 = Hammersmith Infant Neurological Examination - Part 2; HRQoL = health-related quality of life; MAIC = matching-adjusted indirect comparison; OA = onasemnogene abeparvovec; RULM = Revised Upper Limb Module; SMN = survival of motor neuron protein; STC = Simulated Treatment Comparison	

The company concluded that presymptomatic patients receiving risdiplam achieved motor milestones and high levels of motor function after 12 months of treatment, all patients were alive without the need for permanent ventilation, and all could feed orally and swallow.

Risdiplam was reported to be associated with prolonged survival and clinically meaningful improvements in motor function for type 1 patients at the primary endpoints and in longer term analyses up to four years.

For type 2/3 patients, clinically meaningful and statistically significant improvement was reported for MFM32 and RULM scores after 12 months, [REDACTED]. A numerical (but not statistically significant) improvement was reported for HFMSE scores at 12 months.

The registry data, although limited and potentially skewed by poorer baseline characteristics (due to patients being severe enough to be ineligible for nusinersen), suggested that paediatric type 1 patients improved motor function and type 2/3 patients showed an initial improvement followed by stabilisation. For adult patients there were signs of improving or stabilising their upper limb function.

Risdiplam was reported to be well-tolerated up to five years.

[REDACTED]

The EAG notes uncertainty in the evidence due to a lack of controlled trials of risdiplam in presymptomatic and type 1 patients. In particular, without a comparator group it is difficult to be clear how much the treatment is maintaining function or preventing decline compared to natural history, especially for children where growth and consequent increase in weight influences their function and confounds the effect of treatment. However, it appears that

risdiplam has increased survival and achieved positive motor outcomes for people with presymptomatic, type 1, and type 2/3 SMA with no serious safety concerns up to five years.

7.3 Critique of Roche economic models

The EAG reviewed and critically appraised the economic models and the additional information in response to the points for clarification submitted by Roche.^{44,63} In this section, the EAG assesses the company submission against the NICE reference case checklist³³ and then present a critique of the submitted economic model structures and economic evidence used to parameterise these economic models, according to the population groups defined in the decision problem (presymptomatic, type 1 and type 2/3 SMA).^{6,44}

7.3.1 NICE decision problem

The company submission⁴⁴ was evaluated against the NICE reference case checklist³³ and the findings are summarised in Table 40.

Table 40. Comparison of company's and NICE decision problem

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	People with types 0, 1, 2, 3 or 4 5q SMA, or presymptomatic 5q SMA confirmed with genetic testing with 1 to 4 SMN2 copies.	The company submission did not report on type 0 and 5q SMA type 4 because of paucity of evidence to conduct an economic evaluation. The company reported the economic evaluation results separately for presymptomatic SMA, type 1 SMA and type 2/3 SMA populations.
Intervention	Interventions are monotherapies in addition to existing clinical services and established clinical management.	The company assessed cost-effectiveness of risdiplam.
Comparators	Established clinical management in the NHS, including the Best supportive care (BSC) The interventions will be compared to each other In addition, Onasemnogene Apeparvovec (OA) will be used as comparator treatment for children aged 12 months and under with a bi-allelic mutation in the SMN1 gene and present with a clinical diagnosis of type 1 5q SMA or presymptomatically	The company considered nusinersen, OA and BSC as comparators. However, BSC was not considered appropriate comparator for presymptomatic population. In addition, OA was not considered an appropriate comparator for type 2/3 SMA population.

Element of health technology assessment	Reference case	EAG comment on company's submission
	with up to 3 copies of the SMN2 gene.	
Perspective on outcomes	The outcome measures to be considered include: • Motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills) • Bulbar function (including, for example, swallowing and ability to communicate) • Frequency and duration of hospitalisation • Respiratory function • Complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation • Stamina and fatigue • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers)	Presymptomatic: risdiplam/nusinersen/OA: naïve comparison led to the assumption of equivalent efficacy. Motor milestones defined by HINE-2 scores with a continuous time Markov multi-state model fitted to the data of RAINBOWFISH.⁶⁰ Mortality from general population QALYs considered (though any difference nullified). Type 1: Risdiplam vs BSC/nusinersen: motor milestones informed by unanchored MAIC between ENDEAR and FIREFISH⁶⁴ Risdiplam vs OA: motor milestones informed by unanchored MAIC using results from FIREFISH⁵⁶ and STRIVE-EU⁶⁵ Mortality data from FIREFISH⁵⁶ Type 2/3: Risdiplam vs BSC: motor milestones informed by SUNFISH⁵³ Risdiplam vs nusinersen: motor milestones informed by unanchored MAIC from CHERISH²⁸/SUNFISH⁵³ Mortality data: pooled pseudo IPD data from literature for type 2, and general population data for type 3. Bulbar dysfunction, non-permanent respiratory support, scoliosis, considered across populations.

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on costs	Costs will be considered from an NHS and Personal Social Services perspective.	Appropriate
Type of economic evaluation	Cost utility analysis using QALYs. Cost comparison.	Presymptomatic: Cost-comparison for risdiplam vs nusinersen, risdiplam vs OA Type 1 and type 2/3: Cost utility analysis for risdiplam vs nusinersen, risdiplam vs BSC, risdiplam vs OA (only for type 1)
Time horizon	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	Presymptomatic and type 1: ■■■■■ years Type 2/3: ■■■■■
Synthesis of evidence on health effects	Based on systematic review.	Cost-comparison based on naïve comparison results.
Measuring and valuing health effects	Express health effects in QALYs for cost-effectiveness analyses.	Presymptomatic: Assumed equivalent efficacy, QALYs difference assumed to cancel out type 1 and type 2/3: QALYs
Source of data for measurement of health-related quality of life	For the reference case, report the measurement of changes in health-related quality of life directly from patients.	Presymptomatic and type 1: patient HSUVs from TA588 ² and carer HSUVs from Bastida et al. 2017. ⁶⁶ Type 2/3: patient HSUVs from Lloyd et al. 2019 ⁶⁷ and carer HSUVs from Bastida et al. 2017 ⁶⁶ and UK general population utility.
Source of preference data for valuation of changes in health-related quality of life	The utility of these changes should be based on public preferences using a choice-based method.	Appropriate
Equity considerations	No additional equity considerations in the NICE scope.	Appropriate

Element of health technology assessment	Reference case	EAG comment on company's submission
Evidence on resource use and costs	Resource use and cost data should have been identified systematically.	de novo Roche study/ TA588for scenario analysis ²
Discounting	Annual discount rate of 3.5% for costs and outcomes.	Appropriate
Source: Company submission ⁴⁴ and NICE reference case ³³ Abbreviations: BSC = best supportive care; EAG = Evidence Assessment Group; HSUV = health state utility values; MAIC = matching-adjusted indirect comparison; OA = Onasemnogene Abeparvovec; QALY = quality-adjusted life years; SMA = spinal muscular atrophy; SMN= survival motor neuron		

7.3.2 Presymptomatic population

7.3.2.1 Model structure

7.3.2.1.1 Type of model

Roche used a Markov model to represent the natural history of presymptomatic 5q SMA which was primarily informed by the previous NICE TA755 for risdiplam (see Figure 10).³

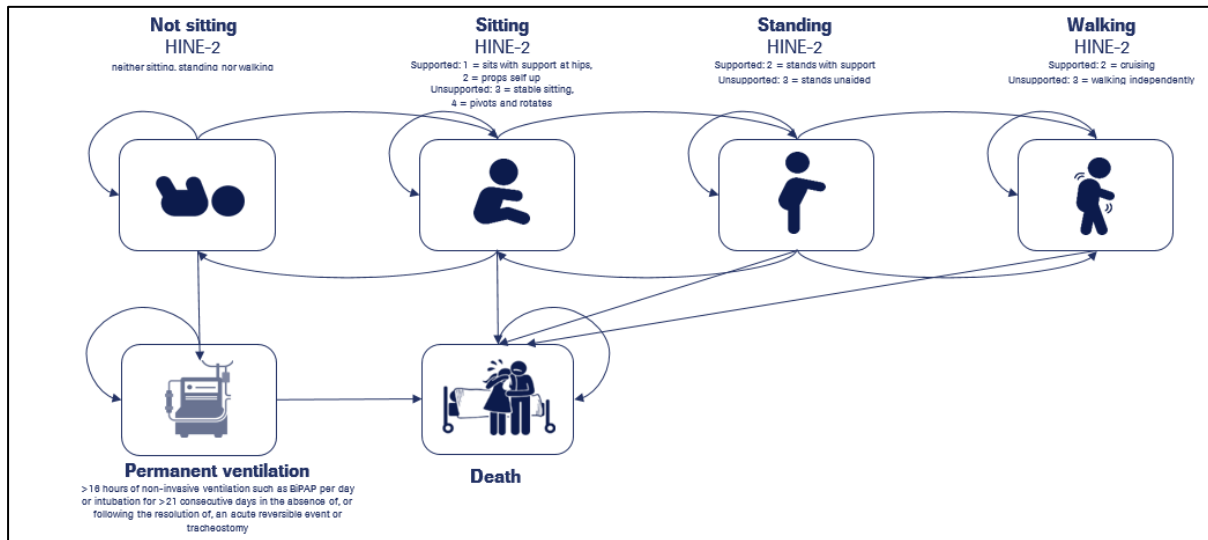
7.3.2.1.2 Health states and transitions

The Markov model was built in Microsoft Excel with four mutually exclusive health states: 'not sitting', 'sitting' (with or without support), 'standing' (with or without support), and 'walking' (with or without support), informed by the items of the HINE-2 scale representing motor milestones.⁴⁴ Patients in the 'sitting' state corresponded to a HINE-2 sitting score of at least 1; the 'standing' state to a minimum HINE-2 standing score of 2; and the 'walking' to a minimum HINE-2 walking score of 2.⁴⁴ The model states and their respective HINE-2 score equivalent used are presented in Table 41. An additional state for 'permanent ventilation' was explicitly included to represent SMA's impact on prognosis and to reflect current clinical practice. The definition of permanent ventilation was informed by the FIREFISH trial as: > 16 hours of non-invasive ventilation per day or intubation for > 21 consecutive days.^{44,54}

Table 41: Model health state definitions based on HINE-2 scores

Model states	HINE-2 score equivalent
Not sitting	< 1 in the HINE-2 sitting dimension
Sitting (with or without support)	≥ 1 in the HINE-2 sitting dimension to <2 standing dimension
Standing (with or without support)	≥ 2 in the HINE-2 standing dimension to <2 walking dimension
Walking (with or without support)	≥ 2 in the HINE-2 walking dimension
Permanent ventilation	> 16 hours of non-invasive ventilation per day or intubation for > 21 consecutive days
Source: prepared by the EAG based on HINE-2 scale Abbreviations: HINE-2 = Hammersmith Infant Neurological Examination — Part 2	

Figure 10: Model structure for presymptomatic and type 1 SMA populations used by Roche



Source: company submission, Document B, Figure 28⁴⁴

Abbreviations: HINE-2 = Hammersmith Infant Neurological Examination — Part 2

Patient data from the single-arm RAINBOWFISH trial with a follow-up of one year were used to inform the transition probabilities in the risdiplam arm.⁵⁷ This independent patient data was fitted using a continuous time Markov multi-state model to generate monthly probabilities of improving, deteriorating, or maintaining motor milestones corresponding to the model health-states.⁴⁴ It was assumed that patients could only improve, maintain, or deteriorate by one motor milestone each month (equivalent to 1 model cycle). Probabilities were estimated for the 2 SMN copies group and the > 2 SMN group, and used a weighted average based on 2 SMN group proportions from RAINBOWFISH.⁵⁷

Table 42 reports the base-case transition probabilities for risdiplam used in the presymptomatic model. The company assumed equal efficacy and utilised the same transition probabilities for nusinersen and OA.

Table 42: Base-case transition probabilities for risdiplam, nusinersen and OA

From\To	Non-sitting	Sitting	Standing	Walking
Non-sitting	■	■	-	-
Sitting	■	■	■	-
Standing	-	■	■	■
Walking	-	-	■	■

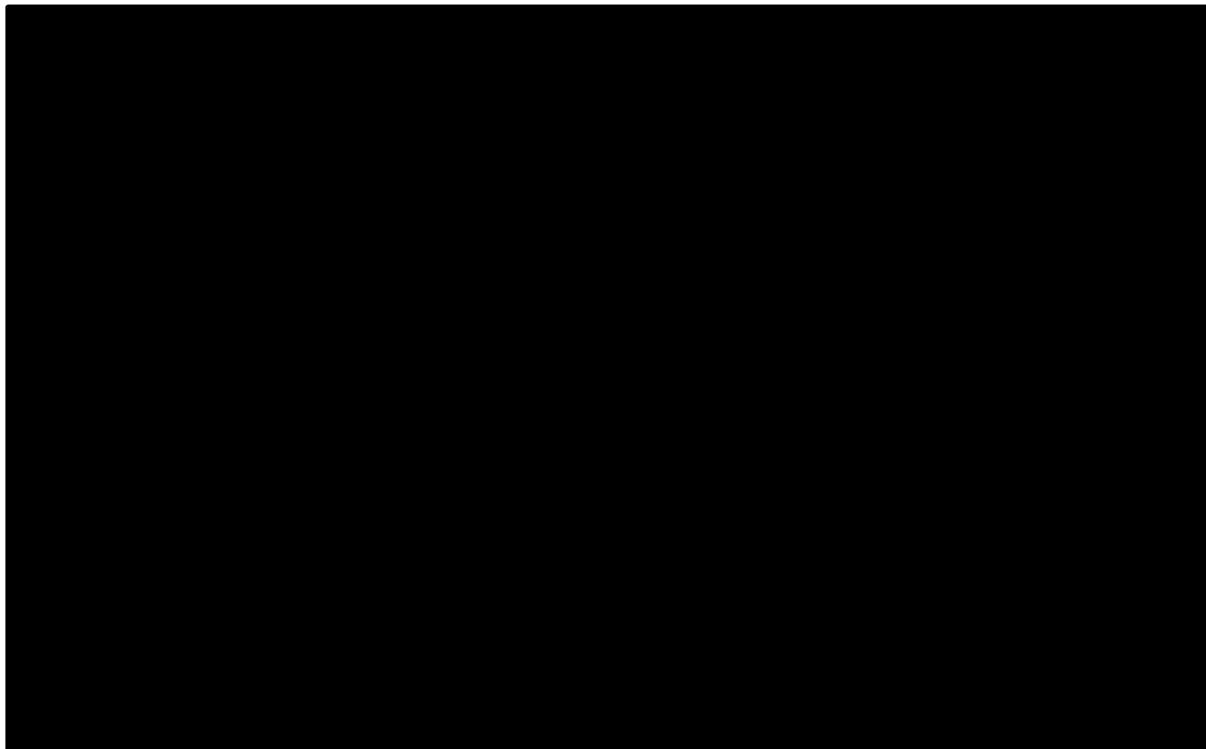
Source: company submission, Document B, Table 106⁴⁴

Abbreviations: HINE-2 = Hammersmith Infant Neurological Examination — Part 2; OA = onasemnogene abeparovector

After the points for clarification, the company detailed that multiple models were tested adjusting for covariates and were assessed for goodness of fit to the study data using the

Akaike Information Criteria (AIC), as well as visual plots.⁶³ Figure 11 shows the visual plots presented by Roche comparing risdiplam trial data with their modelled prediction.

Figure 11: Observed versus multi-state Markov model predicted prevalence for RAINBOWFISH motor milestones (Overall SMN2 copy number, all forward transitions constrained to be equal)



Source: company submission after points for clarification⁶³

Abbreviations: SMN = survival motor neuron

The model assumed that, after 10 years, patients receiving either risdiplam, nusinersen or OA either maintain or improve the motor milestones achieved. BSC was not considered a suitable comparator, therefore it does not feature in the analysis.⁴⁴ Since no events of permanent ventilation were observed during RAINBOWFISH,⁵⁷ it was assumed that patients receiving any disease-modifying therapy were not at risk of moving to permanent ventilation.

EAG comment: The EAG considers the model structure, and company's approach to derive transitions across motor milestones for risdiplam, to be largely appropriate. However, the EAG raises concern about the long-term assumptions of sustained motor milestones during treatment, as clinical feedback indicated that a risk of motor milestone decline may still be present, even with continued treatment.

The EAG chose to align the long-term effectiveness assumptions in the Roche model with those used in the Biogen model to ensure consistency in disease progression over the long-term. This approach assumed that the benefit of disease modifying therapies (DMTs) was not lifelong, instead DMTs enable patients to achieve motor milestone improvements for a period consistent with the available clinical trial evidence. After this period, patients were assumed to either maintain their motor milestones or at risk of gradually losing them over the long-term. For risdiplam treatment effectiveness was assumed to last 72 months by the EAG, similar to the available follow-up data for nusinersen,³⁰ - which is a favourable assumption to risdiplam, given that the follow-up from RAINBOWFISH was only 12 months.⁵⁷

Patients receiving BSC were assumed to gain improvements in motor milestones over the first 12 months, based on Roche's internal natural history data.⁴⁴ Beyond 12 months the rate of motor milestone decline corresponded to the natural history of SMA disease reported by Wadman et al. 2019³⁹ using a disease distribution across SMA types 1, 2, and 3 from Calucho et al. 2018³⁸. For risdiplam, the relative rate of motor milestone decline was assumed to be an average of the rates of decline used in the type 1 and the type 2 and 3 population models.

Table 43 Long-term risk of decline for BSC based on natural history of disease

Long-term decline estimates for BSC	Type 1	Type 2 and 3	Presymptomatic
BSC sitting to not sitting	0.003	0.002	0.002
BSC standing to sitting	0.035	0.025	0.021
BSC walking to standing	0.071	0.051	0.043
Source: produced by the EAG from Wadman et al ³⁹ Abbreviations: BSC = best supporting care			

7.3.2.2 Population

The population modelled reflected the baseline characteristics of RAINBOWFISH trial (see Table 44).⁵⁷

Table 44: Baseline characteristics of the presymptomatic population in the Roche model

Characteristics	Overall (N=18)	SMN2 2 copies (N=7)	SMN2 > 2 copies (N=11)
Age at first dose in days (median (range))	27.33 (7.28)	22.86 (5.37)	30.18 (7.07)
Female (n (%))	10 (55.56%)	3 (42.86%)	7 (63.4%)
Weight (kg(SD))	3.98 (0.7250)	3.76 (0.427)	4.12 (0.853)
SMN2 copies (n(%))			
2 copies	7 (38.89%)	7 (100%)	0 (0%)
3 copies	7 (38.89%)	0 (0%)	7 (63.4%)
≥ 4 copies	4 (22.22%)	0 (0%)	4 (36.36%)
Source: company submission, document B, Table 105 ⁶³ Abbreviations: SD = standard deviation; SMN = survival motor neuron			

7.3.2.3 Interventions and comparators

The presymptomatic model compared risdiplam against nusinersen and OA in a population with the characteristics like those reported above in Section 7.3.2.27.3.2.2.⁶³

Intervention: The company modelled risdiplam as the first-line therapy according to its marketing authorisation as a treatment.^{44,68} In the company's submitted economic model, in line with the marketing authorisation, the patient cohort receiving risdiplam were orally administered a daily dose determined by the patient's age and body weight (see Table 45).

Table 45: Risdiplam dosing regimen

Age	Dose administered
16 days to 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)	5mg
Source: company submission, document B, Table 104 ⁶³ Abbreviations: kg = kilograms; mg = milligrams	

Comparator: The company modelled nusinersen and OA as the comparators for presymptomatic populations. The decision model submitted by Roche included BSC as a comparator based on data from an internal natural history study.⁴⁴ However, the company did not consider BSC a relevant comparator for the presymptomatic population, reasoning that patients are likely to receive a disease modifying therapy upon diagnosis of SMA, therefore overlooking the results comparing risdiplam with BSC.⁴⁴

EAG comment: The base-case submitted by Roche for the presymptomatic population did not include BSC as an appropriate comparator, arguing that in current clinical practice patients diagnosed with SMA are expected to receive a DMT. However, the EAG is concerned about the gaps in clinical evidence that make comparisons between risdiplam and other DMTs highly unreliable.⁶⁹

Considering the limitations in relative effectiveness evidence between DMTs, the EAG decided to focus the economic decision problem in the presymptomatic population on comparing risdiplam against BSC for analytical purposes, while acknowledging that current clinical practice is constantly evolving. Comparisons between risdiplam and other DMTs will be presented as scenario analyses using the evidence available, highlighting the caveats around the potential for bias. As RAINBOWFISH⁵⁷ was a single-arm trial, the EAG relied on internal natural history of disease data from Roche to model BSC.⁴⁴

7.3.2.4 Perspective, time horizon and discounting

The analysis was conducted from the perspective of the NHS and Personal Social Services (taking account of costs directly related to the medical treatment of patients with SMA, and the quality of life of patients with SMA and their carers) and with a time horizon of [REDACTED] (considered to cover the lifetime) in the base case.⁶³ The costs and benefits were discounted at annual rate of 3.5% in accordance with the NICE methods guidelines.⁴⁰

EAG comment: To fully capture the impact of the disease and the interventions across time, the EAG considers a lifetime horizon covering 100 years to be appropriate. In contrast, the [REDACTED] approach used in the company's model risks putting an excessive focus exclusively on the BSC arm and may underestimate the survival gains from treatment.

7.3.2.5 Treatment effectiveness and extrapolation

As detailed above, monthly transition probabilities for risdiplam between motor milestone-based health states were derived from the first year of follow-up of the ITT population in RAINBOWFISH⁵⁷. However, as this was a single-arm trial, in order to model the BSC arm Roche presented data from its own natural history of disease study.⁴⁴ Monthly transition probabilities were derived from this data but it was unclear to the EAG how well patient characteristics matched this population with the RAINBOWFISH⁵⁷ study, and what methodology was used to derive these monthly probabilities. Table 46 reported the monthly transition probabilities used for BSC.

Table 46: Monthly transition probabilities for the BSC arm for the presymptomatic population in the Roche model

From\To	Non-sitting	Sitting	Standing	Walking
Non-sitting			-	-
Sitting				-
Standing	-			
Walking	-	-		

Source: EAG extracted data from company submitted models

The company presented the results of a series of naïve comparisons between risdiplam and nusinersen using results from RAINBOWFISH⁵⁷ and NURTURE³⁰ across HINE-2 and BSID-III.⁶³ As these comparisons were not controlled by confounders and results were not statistically different, the model assumed there was evidence of equivalent effectiveness with nusinersen.⁶³ Similarly, a naïve comparison between risdiplam and OA using BSID-III results from RAINBOWFISH⁵⁷ and SPR1NT was conducted, where no statistically significant difference was found.⁶³ Therefore, equivalent effectiveness was also assumed between risdiplam and OA.⁶³

EAG comment: The EAG questions the conclusion that an absence of statistically significant differences in mobility scores from a naïve comparison alone, is evidence of equivalence in effectiveness across DMTs. While the EAG acknowledges the gaps in comparative data for this population, it remains unclear whether a cost-comparison approach was appropriate to assess the impact of uncertainty in clinical effectiveness across treatments.⁷⁰

Although the EAG's base-case analysis compared risdiplam with BSC, the EAG conducted a scenario analysis using CUA to compare the DMTs. While the EAG was unable to use the naïve comparison data for OA, the approach assumed a degree of uncertainty around the assumption of equivalent effectiveness. The EAG also explored scenario analysis using the naïve comparison estimates between risdiplam and nusinersen.

7.3.2.6 Health related quality of life

Patient Health-Related-Quality of Life (HRQoL) data was collected neither from RAINBOWFISH⁵⁷ nor FIREFISH.⁵⁶ To model HRQoL in presymptomatic and Type 1 SMA patients, the company relied on the health state utility values from TA755,³ which themselves were based on Lloyd et al 2019⁶⁷ and TA588^{16,44}. Additional scenario analyses were presented using alternative utilities from TA588² and Lloyd et al. 2019.⁶⁷ See Table 47 for the base-case utility values in the model.

Table 47: Utility values used in the Roche economic model for presymptomatic and Type 1 SMA

Roche model base-case			Scenario 1		Scenario 2	
Model health state	Mean utility	Source	Mean utility	Source	Mean utility	Source
Permanent ventilation	-0.02	TA755 and UK clinical experts ³	-0.330	Lloyd et al. 2019 ⁶⁷	-0.240	TA588 ²
Not sitting	0.10		-0.120		-0.120	
Sitting	0.20		-0.040		-0.105	
Standing	0.70		0.375		0.375	
Walking	0.85		0.615		0.615	

Roche model base-case			Scenario 1		Scenario 2	
Model health state	Mean utility	Source	Mean utility	Source	Mean utility	Source
Source: Company submission, document B, Table 121, Table 122 and Table 123 ⁴⁴						
Abbreviations: TA = Technology appraisal						

The base-case analysis submitted by the company combined both patient and carer quality of life for informal carers in the same analysis.⁴⁴ Carer utilities in the base-case analysis depended on the patient health state in the model (Table 48); carer utilities at the not sitting state were taken from TA588², sourced from Bastida et al. 2017,^{2,66} while carer utilities at the walking state were assumed to be equivalent to general utilities in the UK population, with values validated by clinical experts. Roche also conducted a burden of illness study, but the results were deemed to lack clinical validity, these estimates were used as a scenario analysis instead.⁴⁴ The analysis also assumed an average of 2.2 informal carers needed per patient based on internal data.⁴⁴ Finally, the model presented assumed direct increase in utility from therapy at the 'not sitting' and 'sitting' health-states of 0.2 for patients and 0.05 for carers.

Table 48: Carer utilities used in the company model

Patient health-state	Base-case carer utility	Source	Alternative values	Source
PV	0.484	TA588 based on Bastida et al. 2017 ⁶⁶	0.633	Roche UK burden of illness study ⁴⁴
Not sitting	0.484		0.751	
Sitting	0.628		0.737	
Standing	0.771		0.72	
Walking	0.915		0.754	
Source: Company submission, document B ⁴⁴				
Abbreviations: PV = permanent ventilation; TA = technology appraisal				

EAG comment: The EAG recognises that finding utility values for young people is especially challenging. In this scenario our concerns surrounded the critiques that have been made in TA588² regarding the face validity of patient utility estimates used for this appraisal. Therefore, the EAG has adopted the approach used in a more recent appraisal for OA in presymptomatic patients (HST24¹⁶).

The EAG was also concerned about the negative utility value for permanent ventilation, which could be interpreted as worse than being dead, as utility values generally anchor dead at 0; after our consultation with a clinical expert, it was considered that it could send a problematic message to both clinicians and patients. Using an approach from HST24 assumes that utility at permanent ventilation is equal to 0, which the EAG recognises is still not an ideal situation as patients are still alive despite being at a severe health-state.¹⁶

In the presence of negative health-state utilities for the scenario analysis, the EAG has assumed that negative utility values are equivalent to 0 (i.e. equivalent but not worse than death). Regarding the direct impact of disease-modifying therapies, the EAG has assumed these provide an increment of 10% above the mean utility across all health-states where treatment is delivered, to make our analysis consistent across both company submissions.

The EAG was concerned about the approach for combining both patient and informal carer quality of life in the base-case analysis. The data on informal carer utility was not the result of data collection in the clinical trials, and it was difficult to ratify its validity beyond clinical expert opinion. Moreover, as the critique from the Biogen submission showed, there is a lack of a standardised methodology to include carer quality of life (see Section 6.3.2.6).

The EAG understands the importance of the perspective of informal carers in SMA and the value of including the impact on informal carers in this appraisal. For transparency and clarity in our analyses the EAG focused its base-case analysis exclusively on patient quality of life. An additional scenario analysis was presented including treatment impacts on patient and informal carer quality of life with the aim of exploring the potential impact of treatment on both patients and informal carers. This scenario assumed 1 carer on average for consistency with the Biogen analysis, where carer utilities and average carer characteristics were extracted from a recently published study by Lo et al, 2022.⁷¹

The EAG has also updated the approach used to adjust utility values based on age and gender based on the general UK population using the latest advice from the NICE methods guidelines and the latest DSU guidance.⁷²

7.3.2.7 Resource use and costs

The list price used for one 60 mg/80 ml vial of risdiplam was £7,900.⁴⁴ A simple PAS discount of [REDACTED] was applied to the price of risdiplam for a total of [REDACTED].⁴⁴ While a majority of patients receive risdiplam via homecare which is covered by Roche, it was assumed that a small proportion of patients ([REDACTED]) receive risdiplam during hospital care through a pharmacist.⁴⁴

In line with the SmPC, the economic model for presymptomatic and type 1 SMA patients also assumed that patients <2 years old require an average monthly dose of 0.2 mg/kg (of bodyweight) until they reach the age of 2 years, followed by a monthly dose of 0.25 mg/kg of bodyweight until they reach a bodyweight of 20 kg (approximately [REDACTED] of age predicted in the model). Above a bodyweight of 20 kg patients receive a monthly dose of risdiplam of 5 mg. Trial data and natural history of disease studies were pooled to generate patient weight estimates. Relative dose intensity was assumed to be equal to the FIREFISH part 2 trial at [REDACTED].⁴⁴

Comparator interventions resource use: List prices were used for nusinersen at £75,000 per one 12 mg/5 ml vial. Hospital administration costs were derived from an NHSE annual tariff of £10,815.⁴⁴ Nusinersen is administered via 4 loading doses during the first 2 months, and a maintenance dose every 4 months. For OA, a single cost including both administration and drug cost of £1,600,081 was applied.

Health-state related resource use: Roche reported the results of its own Delphi panel study collecting expert opinion on quantitative estimates for health-care resource use (HCRU) related to the management of SMA Type 1 and Type 2/3.⁴⁴ Results showed that resource use was high in SMA patients, particularly regarding disease-related healthcare visits, surgeries, and procedures. Costs from NHS reference values were used to derive monthly costs for each motor milestone-related health state. Resource use values from TA588 were used as a scenario analysis.² The health state related costs used in the models were same for presymptomatic and type 1 populations (Table 49).

Table 49: Monthly health-state related costs applied to the presymptomatic and Type 1 Roche models

Costs per cycle: base-case				Costs per cycle from TA588 ²
Health state	Paediatric patient	Adult patient	One-off costs	Paediatric and adult
Permanent ventilation	£1,557	£761	£15,834	£23,247
Unable to sit	£1,966	£697	£15,547	£13,284
Sitting	£1,504	£521	£12,964	£9,704
Standing	£989	£189	£7,359	£1,951
Walking	£414	£121	£3,702	£1,951

Source: company submission, document B, Table 134⁴⁴

EAG comment: The EAG acknowledges the Roche's effort to use HES data to derive health-state costs for the model, recognising the challenges of generating motor milestone-related resource use estimates for SMA outside of trial data and adapting them to the UK context. However, the EAG is concerned about the substantial differences in monthly costs between TA588² and those used for the base-case analysis derived from the Delphi panel; and the EAG considers this to reflect the uncertainties around the cost of disease in SMA that were highlighted in TA588.²

To maintain consistency with the current company submission and previous SMA appraisals, the EAG used health state costs from the latest NICE submission in this area (HST24).¹⁶ The EAG also explored the costs from the Roche study as a scenario analysis, and acknowledges this as a key area of uncertainty, given the treatment has a direct impact in total patient costs particularly between the 'not sitting' and 'sitting' health states.

7.3.2.8 Adverse events

The company did not include the costs associated with adverse events in the model.⁴⁴ This was informed by RAINBOWFISH⁵⁷, FIREFISH⁵⁶, and SUNFISH⁵³ which had less than 5% of severe treatment-related adverse events.⁴⁴ The economic model did include the impact of non-permanent respiratory support and bulbar dysfunction as disease-related events for the BSC arm only, using data from an SMA natural history study conducted by Roche.⁴⁴

EAG comment: The EAG was concerned about potential double counting of disease-related events in patient HRQoL, particularly for BSC, since the health-state utility values are expected to already reflect the impact of the disease on the general SMA patient population. Additionally, the data used to model these impacts on patient HRQoL was neither derived from clinical trial data nor was validated by clinicians, and therefore raises the risks of underestimating the patient HRQoL values. To ensure consistency across economic models, the EAG assumed that the utility values for each motor milestone fully captures the impact of the disease and related events.

7.3.2.9 Survival

During the first-year follow-up of RAINBOWFISH⁵⁷, no events related to permanent ventilation, or death were observed. The base-case assumed that DMTs did not carry a risk of permanent

ventilation, while survival was assumed to correspond with the UK general population. Therefore, all DMTs had the same survival rates.

EAG comment: Since the EAG has opted for a decision problem comparing risdiplam with BSC, patients in the BSC arm were assumed to be at risk of progressing to permanent ventilation or experiencing an increased mortality risk related to the severity of SMA. Furthermore, the EAG also considered that the Roche approach to modelling overall survival did not adequately capture the increased mortality risks associated with high disease severity.

To address these concerns, and improve consistency in the economic evidence for SMA, the EAG adopted a similar approach to that used in the Biogen submission. This approach assumed an increased mortality risk for patients in the 'permanent ventilation', 'not sitting', and 'sitting' health states. These assumptions were informed by digitised survival curves from the latest NICE submission looking at presymptomatic patients treated with OA (HST24¹⁶).

7.3.2.10 Discontinuation

As no discontinuation events were observed during the RAINBOWFISH trial, treatment discontinuation was not included explicitly in the economic model.^{44,57} This assumption was extended to nusinersen. OA only requires a single delivery; therefore, discontinuation assumptions did not apply to it.

EAG comment: Although the EAG disagrees with the notion that discontinuation from risdiplam is clinically implausible, particularly given known concerns such as potential impacts on fertility, it acknowledges that there is an evidence gap on long-term discontinuation rates. In the absence of long-term discontinuation data, the EAG's economic model maintained the assumption of no discontinuation for either risdiplam or nusinersen, recognising this is a favourable assumption to both therapies.

7.3.2.11 Decision modifier: Severity

The base-case analysis presented comparing risdiplam with BSC met the criteria for a severity multiplier of 1.7 on the incremental QALYs; however, the BSC was not considered a relevant comparator in the presymptomatic population as almost all patients do get treated.⁴⁴

EAG comment: Since BSC was not considered a relevant comparator and risdiplam's independent comparisons with nusinersen and OA were a cost-comparison only, a severity modifier for incremental QALYs would not have impacted the results in the presymptomatic model. In its submission, the company applied the severity modifier to its base-case risdiplam versus BSC analysis, which also included carer utilities.⁴⁴ The EAG considered the application of severity modifier while also including care utilities inappropriate, as the severity modifier should be applied solely on patient utility values. Therefore, the EAG has reported the company results, while also reporting separate results for informal carers and with the use of the severity modifier on patients' utilities only.

7.3.2.12 Company's cost-effectiveness results (presymptomatic population)

Deterministic results from the Roche base-case analysis (based on risdiplam PAS prices and list prices for comparators) showed that risdiplam was [REDACTED] compared to nusinersen, and risdiplam was [REDACTED] compared to OA (Table 50). The comparison with BSC was deemed to be not applicable for this population, but model results suggested risdiplam was [REDACTED] compared to BSC with an ICER of [REDACTED]. Removing the severity modifier from the patient and carers scenario led to an ICER of [REDACTED] (Table 51). Applying

the severity modifier to patient utilities only led to an ICER of [REDACTED] (Table 52). The probability of risdiplam being cost-effective at a WTP of £30,000/QALY was [REDACTED].

Table 50: Deterministic and probabilistic results for the presymptomatic population reported in the Roche submission (using risdiplam PAS price)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/ QALY)
Deterministic							
Risdiplam	[REDACTED]	18.64	[REDACTED]	-	-	-	-
Nusinersen	[REDACTED]	18.64	[REDACTED]	[REDACTED]	0	0	[REDACTED]
OA	[REDACTED]	18.64	[REDACTED]	[REDACTED]	0	0	[REDACTED]
BSC*	[REDACTED]	13.95	[REDACTED]	[REDACTED]	4.7	[REDACTED]	[REDACTED]
Probabilistic							
Risdiplam	[REDACTED]	-	[REDACTED]		-	-	-
Nusinersen	[REDACTED]	-	[REDACTED]	[REDACTED]	-	[REDACTED]	[REDACTED]
OA	[REDACTED]	-	[REDACTED]	[REDACTED]	-	[REDACTED]	[REDACTED]
BSC*	[REDACTED]	-	[REDACTED]	[REDACTED]	-	[REDACTED]	[REDACTED]
*BSC not deemed relevant for Roche's Base-case decision problem Source: Company submission ⁴⁴ Abbreviations: BSC = best supportive care; LY = life years; OA = onasemnogene abeparvovec; QALY = quality-adjusted life year							

Table 51: Deterministic results using carer utilities without the severity modifier (with risdiplam PAS price)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Deterministic							
Risdiplam	[REDACTED]	18.64	[REDACTED]	-	-	-	-
Nusinersen	[REDACTED]	18.64	[REDACTED]	[REDACTED]	0.00	0.00	[REDACTED]
OA	[REDACTED]	18.64	[REDACTED]	[REDACTED]	0.00	0.00	[REDACTED]
BSC	[REDACTED]	13.95	[REDACTED]	[REDACTED]	4.70	[REDACTED]	[REDACTED]
Source: Company submission ⁴⁴ Abbreviations: BSC = best supportive care; LY = life years; OA = onasemnogene abeparvovec; QALY = quality-adjusted life year							

Table 52: Deterministic results using patient utilities with the severity modifier (with risdiplam PAS price)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
<i>Deterministic</i>							

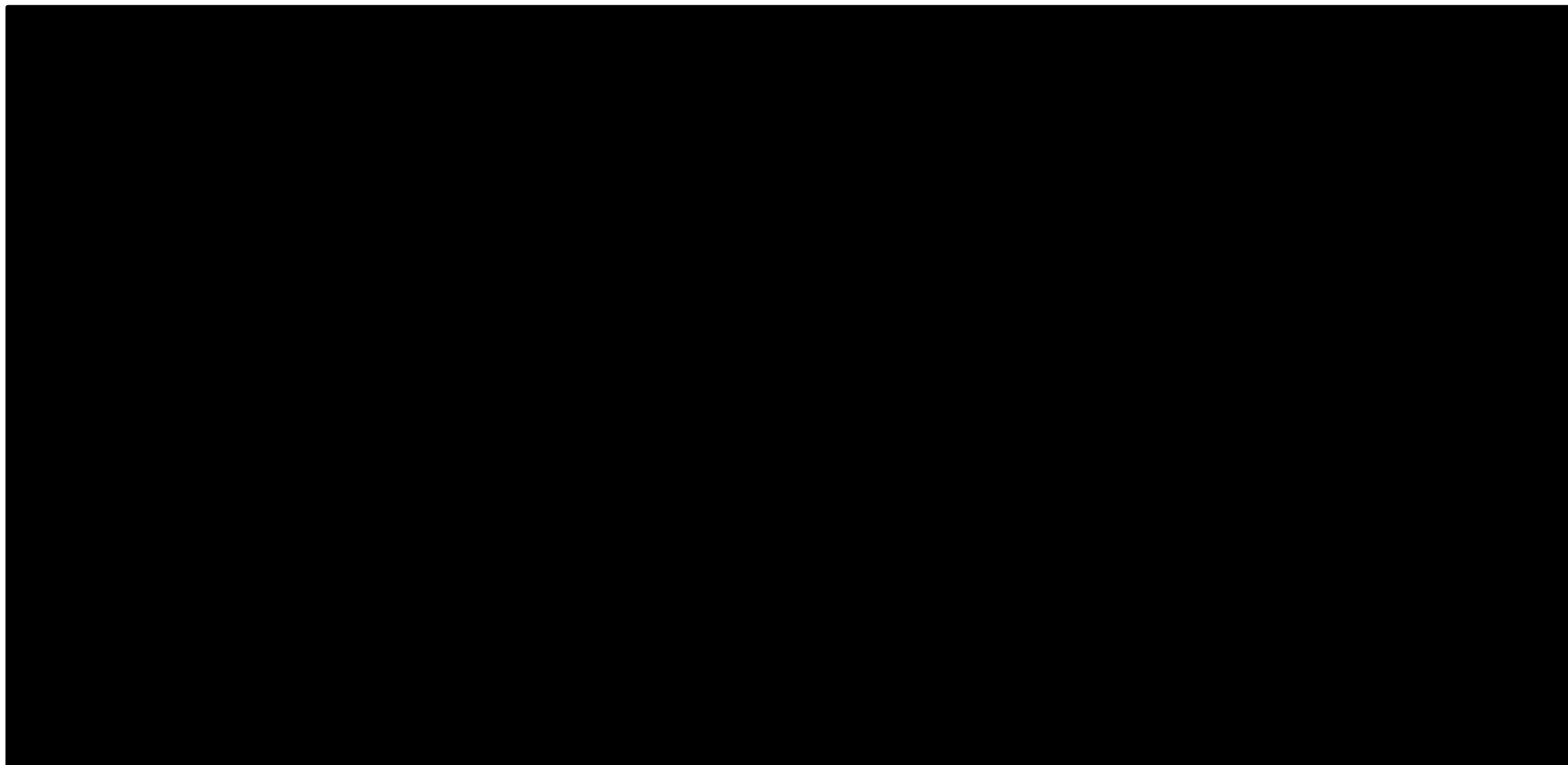
Risdiplam	██████	18.64	████	-	-	-	-
Nusinersen	██████	18.64	████	██████	0.00	0.00	██████████
OA	██████	18.64	████	██████	0.00	0.00	██████████
BSC	██████	13.95	████	██████	4.70	████	██████
Source: Company submission ⁴⁴ Abbreviations: BSC = best supportive care; LY = life years; OA = Onasemnogene Apeparvovec; QALY = quality-adjusted life year							

7.3.2.12.1 Deterministic sensitivity analysis (presymptomatic population)

Risdiplam versus nusinersen

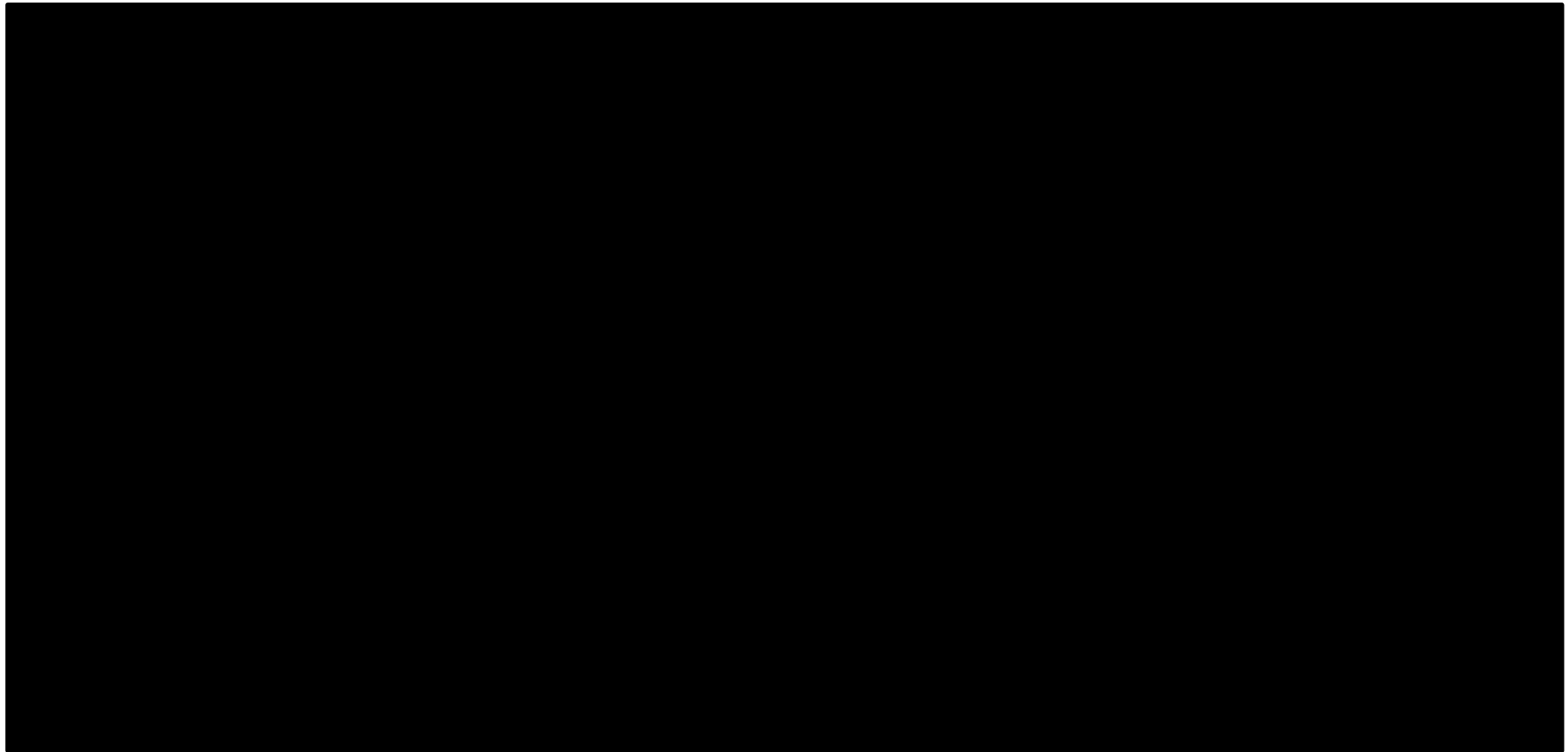
For the comparison between risdiplam and nusinersen parameters with the biggest impacts on cost were drug related costs for nusinersen and risdiplam. Parameters that can have an impact on quality of life between risdiplam and nusinersen were differences in patient utility at 'sitting' and 'not sitting' followed by carer utility at 'sitting' and 'not sitting'.

Figure 12: Deterministic sensitivity analysis on incremental costs: risdiplam versus nusinersen (presymptomatic)



Abbreviations: p.a = per annum; RDI = relative dose intensity

Figure 13: Deterministic sensitivity analysis on incremental QALYs: risdiplam versus nusinersen (presymptomatic)

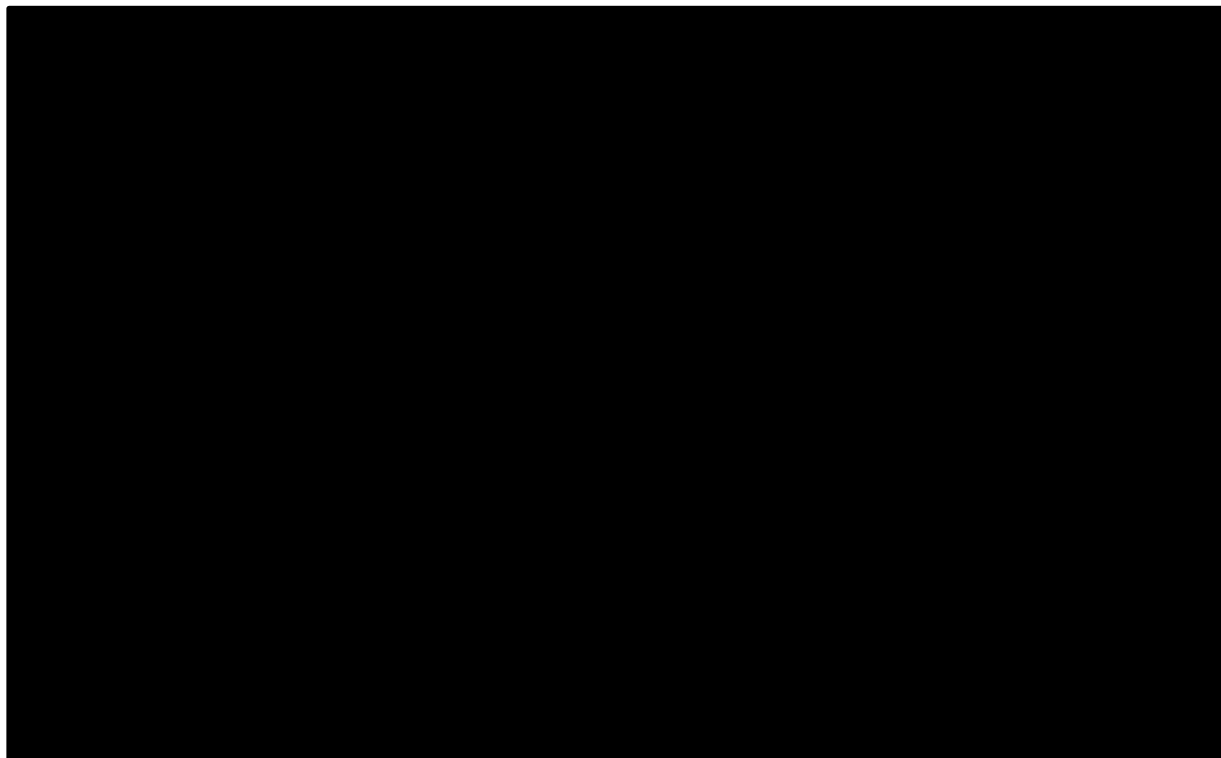


Abbreviations: p.a = per annum; QALY = quality-adjusted life year

Risdiplam versus OA

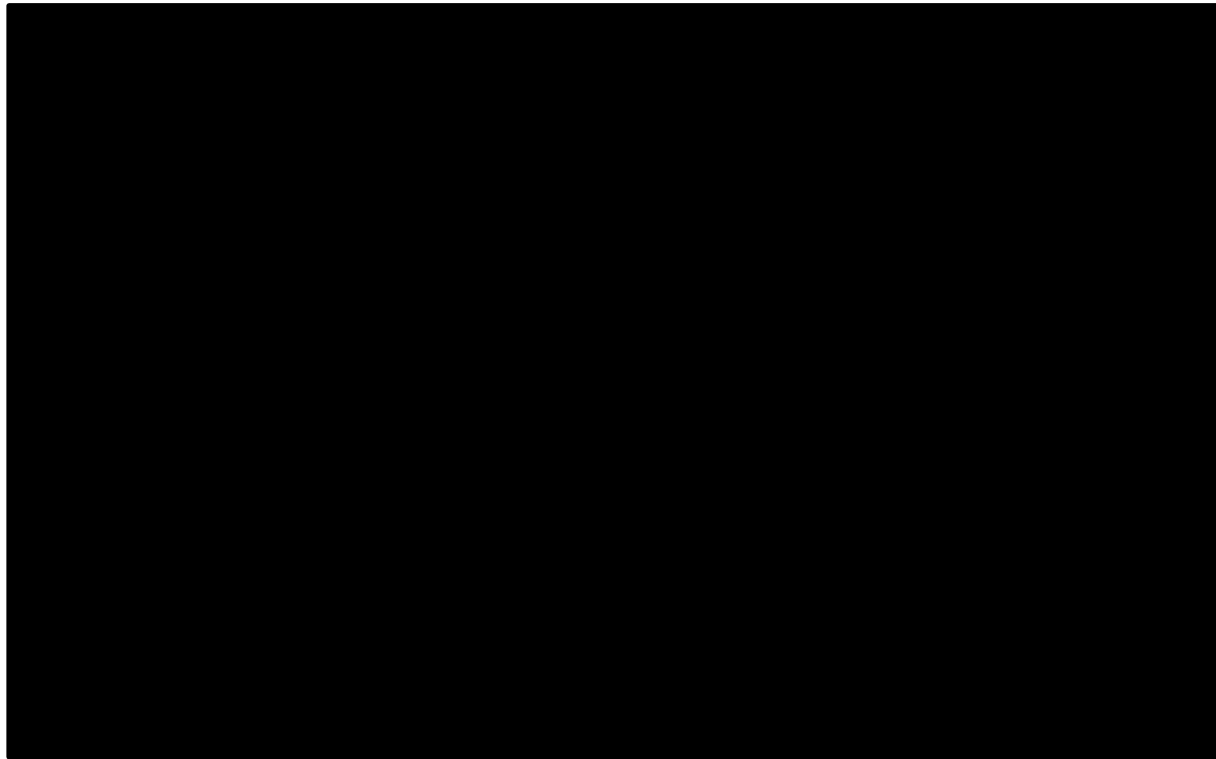
For the comparison between risdiplam and OA parameters with the biggest impacts on cost were drug related costs for risdiplam and OA. Parameters that had an impact on quality of life between risdiplam and OA were differences in patient utility at “sitting” and “not sitting” followed by carer utility at “sitting” and “not sitting”.

Figure 14: Deterministic sensitivity analysis on incremental costs: risdiplam versus OA (presymptomatic)



Abbreviations: kg = kilograms; p.a = per annum; RDI = relative dose intensity; OA = onasemnogene abeparvovec

Figure 15: Deterministic sensitivity analysis on incremental QALYs: risdiplam versus OA (presymptomatic)

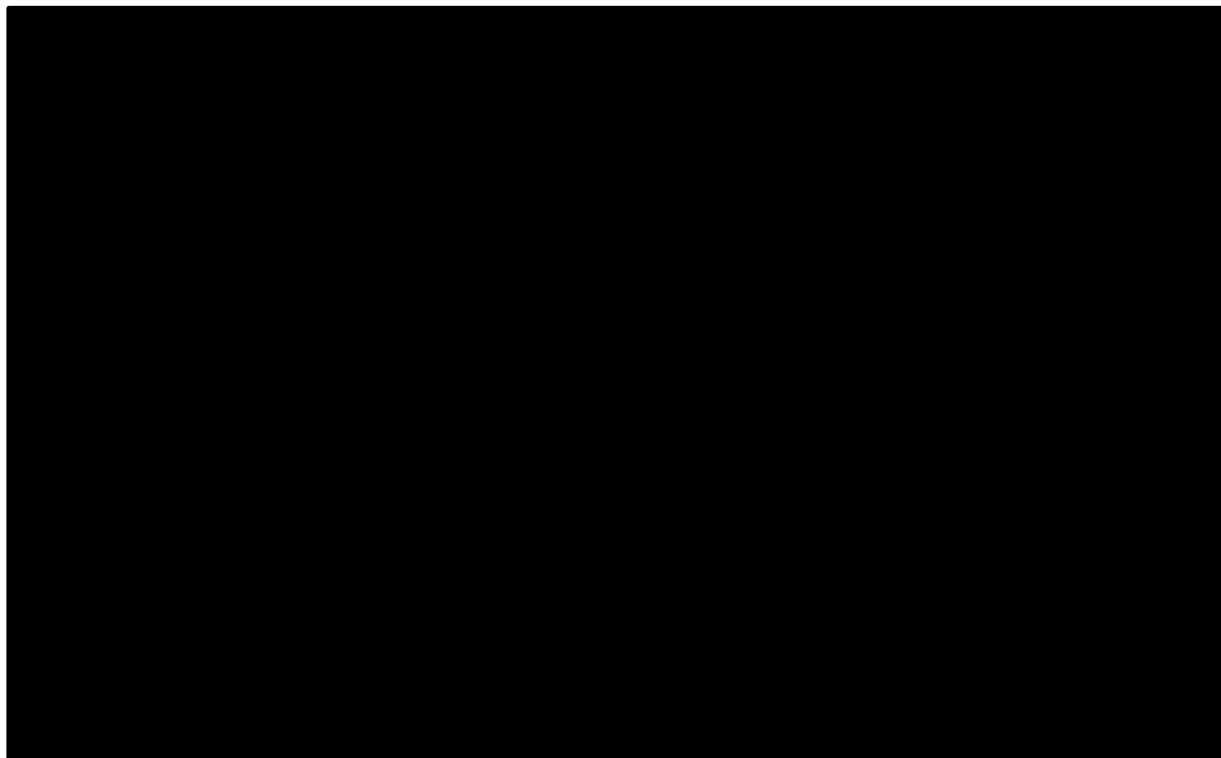


Abbreviations: p.a = per annum; QALY = quality-adjusted life year; OA = onasemnogene abeparvovec

Risdiplam versus BSC

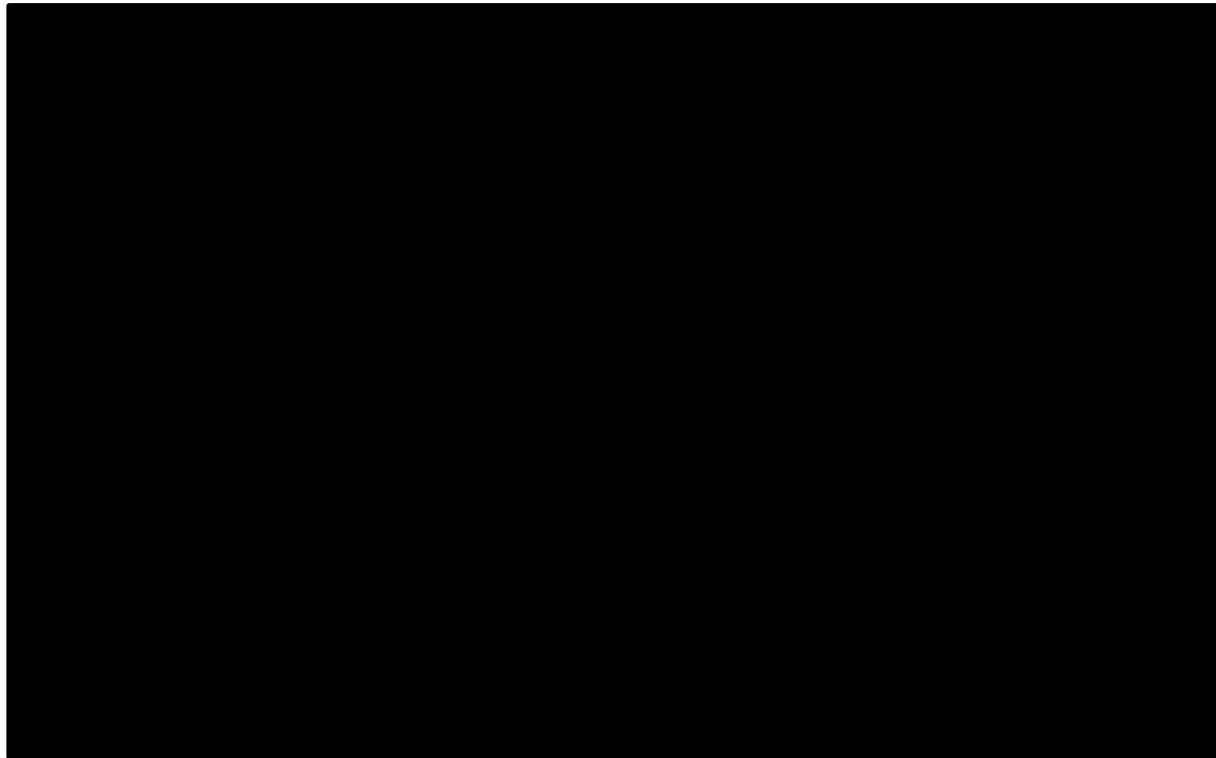
For the comparison between risdiplam and BSC parameters with the biggest impacts on cost were drug related costs for risdiplam, and disease-related costs for children at 'sitting' and 'not sitting' health states. Parameters that had an impact on quality of life between risdiplam and BSC were differences in patient and carer utilities at 'walking' and the number of carers.

Figure 16: Deterministic sensitivity analysis on incremental costs: risdiplam versus BSC (presymptomatic)



Abbreviations: BSC = best supportive care; RDI = relative dose intensity

Figure 17: Deterministic sensitivity analysis on incremental QALYs: risdiplam versus BSC (presymptomatic)



Abbreviations: BSC = best supportive care; HSUV = health state utility value; QALY = quality-adjusted life year

7.3.2.12.2 Company's scenario analysis (presymptomatic population)

The scenario analysis showed that for the cost comparisons between risdiplam and nusinersen and risdiplam and OA the largest impact on costs were changes to the discount rates, and including VAT savings from risdiplam home care. For the comparison with BSC the largest impacts were from changing the source data for BSC, changing resource use to values from TA588, and changing caregiver utilities.

Table 53: Results of Roche's scenario analysis (presymptomatic population)

Scenario	ICER vs BSC	% ICER change	Incremental costs vs nusinersen	% change	Incremental costs vs OA	% change
Base case	████	-	██████	-	██████	-
Efficacy scenarios						
Comparative efficacy vs. BSC: Source for BSC set to PNCR data with SMN2 copies matched to RF	████	████	██████	█	██████	█
Source for % scoliosis: change to Wijngaarde et al 2019 ³⁶	████	████	██████	█	██████	█
Source for % bulbar dysfunction: change to Wadman et al 2017 ³⁹	████	████	██████	█	██████	█
Source for % respiratory support: change to van der Heul et al 2019 ⁷³	████	████	██████	█	██████	█
HCRU scenarios						
Alignment with TA588 source for HCRU ²	████	████	██████	█	██████	█
Alignment with TA588 source for HCRU and PV health state costs: 175% increase from the "Not Sitting" health state ²	████	████	██████	█	██████	█
Utility values scenarios						
Source for patient utility values: EQ-5D-3L (NICE ERG TA588) ²	████	████	██████	█	██████	█
Source for patient utility values: EQ-5D-Y (Lloyd et al., 2019) ⁶⁷	████	████	██████	█	██████	█
Source for caregiver utility values: Roche utility survey	████	████	██████	█	██████	█
Source for caregiver utility values: UK Burden of Illness Study	████	████	██████	█	██████	█
Other Scenarios						
Inclusion of VAT saving from risdiplam homecare	████	████	██████	████	██████	████
Number of carers lowered to 2	████	████	██████	█	██████	█
Number of carers increased to 3	████	████	██████	█	██████	█

Scenario	ICER vs BSC	% ICER change	Incremental costs vs nusinersen	% change	Incremental costs vs OA	% change
Discount rate for both costs and benefits is lowered to 1.5%	■	■	■	■	■	■
Discount rate for benefits is lowered to 1.5%, discount rate for costs remains 3.5%	■	■	■	■	■	■

Source: Company submission⁴⁴
Abbreviations: BSC = best supportive care; HCRU = health care resource use; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; OA = onasemnogene abeparvovec; TA = technology appraisal; UK = United Kingdom; VAT = value added tax

7.3.3 Type 1 SMA population

7.3.3.1 Model structure

7.3.3.1.1 Type of model

Same as the presymptomatic model (see section 7.3.2.1)

7.3.3.1.2 Health states and transitions

Model health states and motor milestones definition same as presymptomatic model (see Section 7.3.2.1.2)

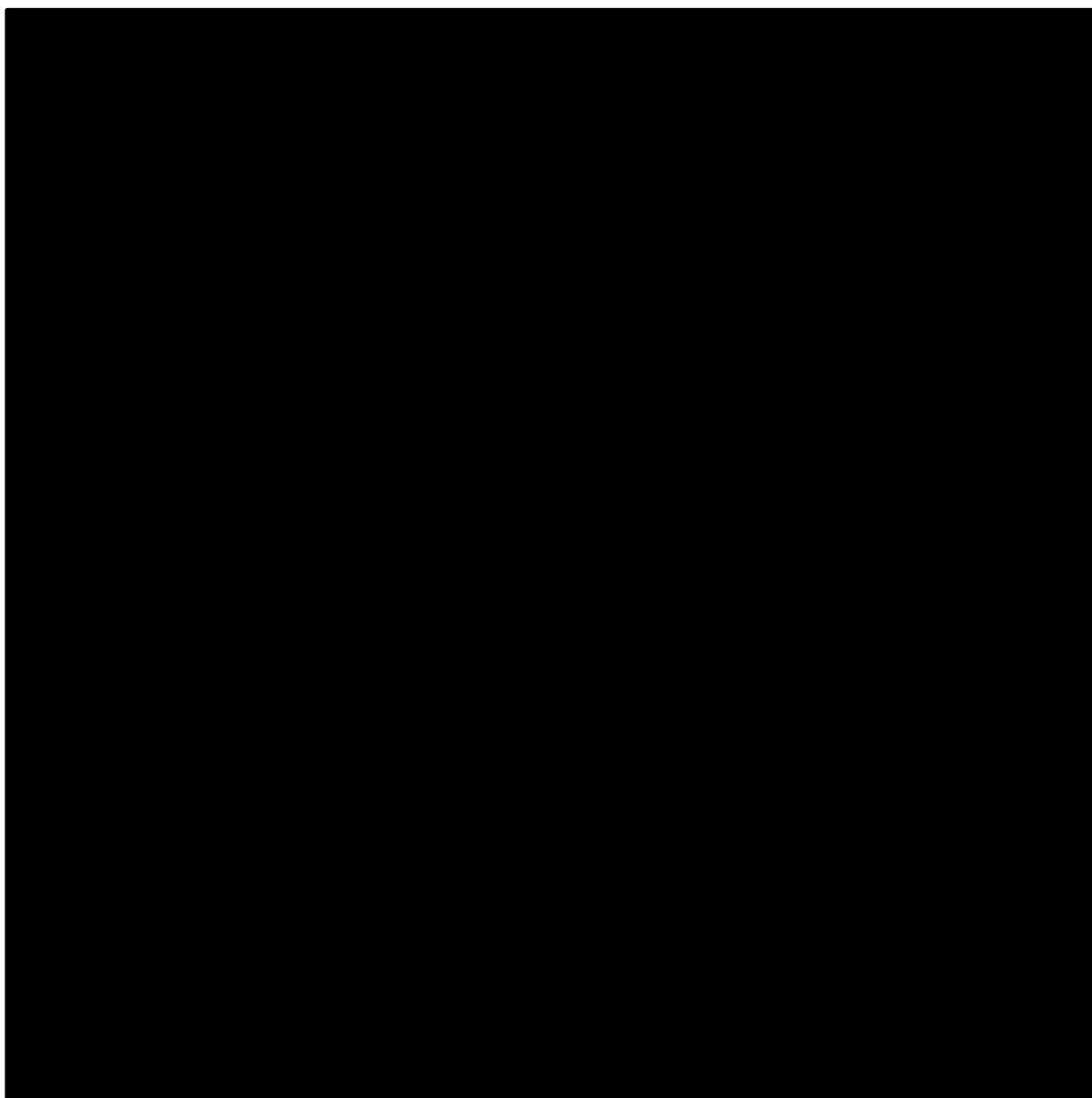
In addition, transition probabilities for the risdiplam arm were based on the 48-month follow-up data from the FIREFISH trial.⁵⁴ Data were fit into a continuous time Markov multi-state model, using baseline HINE-2 score as a covariate for transitions between 'not sitting' and 'sitting'. Transition probabilities were adjusted to only allow an improvement or loss of a single motor milestone (as captured in the model states) per 1 month model-cycle. After the points for clarification letter, the company detailed that multiple models were tested adjusting for covariates and were assessed for goodness of fit to the study data using AIC scores, as well as visual plots.⁶³

Table 54: Monthly transitions probabilities for risdiplam based on the selected continuous time Markov multi-state model using HINE-2 defined motor milestones from the FIREFISH population

From\To	Non-sitting	Sitting	Standing	Walking
Non-sitting	■	■	■	■
Sitting	■	■	■	■
Standing	■	■	■	■
Walking	■	■	■	■

Source: company submission, document B⁴⁴
Abbreviations: HINE-2 = Hammersmith Infant Neurological Examination — Part 2

Figure 18: Observed versus multi-state Markov model predicted prevalence for FIREFISH motor milestones (HINE-2)



Source: company submission⁴⁴

After 66 months (5.5 years) risdiplam and nusinersen patients were assumed to maintain or improve the motor milestones captured by the model states. OA patients were assumed to have continued treatment effectiveness, while patients not receiving disease-modifying treatments and BSC were at risk of losing motor milestones. Since FIREFISH was a single-arm trial, transition probabilities for BSC, nusinersen, and OA were based on the unanchored MAIC analysis.^{54,64}

EAG comment: The EAG considers the model structure, and the approach used by the company to derive transitions across motor milestones for risdiplam to be appropriate for the decision. Long-term assumptions of maintenance of motor milestones under treatment were

of concern to the EAG, as clinical feedback suggested that long-term risks of motor decline may be present even during treatment.

The EAG decided to align the approach to long-term effectiveness in the Roche model with that of the Biogen model to ensure consistency in the assumptions of disease progression over the long-term. This meant that the effect of disease modifying therapies was not lifelong, instead DMTs allow patients to reach motor milestone improvements for a duration of time that matches the available clinical trial evidence. After this period, patients either maintain their motor milestones or are at risk of losing them over the long-term. For risdiplam this was 60 months of motor milestone improvement based on FIREFISH trial data.⁵⁴

Patients receiving BSC were assumed to gain improvements in motor milestones over the first 12 months based on FIREFISH trial data and the unanchored MAIC estimates with ENDEAR.^{54,64} After 12 months the rate of motor milestone decline corresponds to the natural history of SMA disease reported by Wadman et al. 2019.³⁹ The relative rate of motor milestone decline for risdiplam was extracted from Ribero et al. 2022 which reports that 80% of risdiplam patients are treatment responders compared to BSC.⁶⁴

7.3.3.2 Population

FIREFISH baseline characteristics: mean age at baseline was 0.48 years, mean bodyweight at baseline was 5kg and 57% were females.⁵⁴

7.3.3.3 Interventions and comparators

The type 1 SMA model compared risdiplam against nusinersen, BSC and OA in a population with characteristics like those reported above in section 7.3.3.2.

Intervention: Same as the presymptomatic model (see Section 7.3.2.3)

Comparators: Same as the presymptomatic model (see Section 7.3.2.3), however, unlike the presymptomatic model, the type 1 model also used BSC as a comparator in addition to nusinersen and OA.

EAG comment: In line with the critique of the clinical evidence and the limitations of the comparative effectiveness analysis, the EAG's base-case economic analysis focused on comparing risdiplam with BSC. As FIREFISH was a single-arm trial, the comparative analysis relied on estimates derived from the unanchored MAIC between FIREFISH and ENDEAR to inform the BSC arm;^{54,64} the EAG recognises the limitations of this approach, given the small sample size and presence of confounding variables that could not be adequately adjusted for in the indirect comparison.⁶⁹

7.3.3.4 Perspective, time horizon and discounting

Same as the presymptomatic model (see Section 7.3.2.4)

EAG comment: In order to fully capture the impact of the disease and the interventions across time, the EAG considers a lifetime horizon covering 100 years to be appropriate, as the [REDACTED] approach selected by the company risks putting an excessive focus exclusively on the BSC arm and not accounting for survival gains from treatment.

7.3.3.5 Treatment effectiveness and extrapolation

It was not clear from the report how the BSC arm was modelled. The company submission reported that ITC estimates used in TA755 for BSC were used in their current model³ however,

the EAG was not able to corroborate this as the information is marked as confidential in the public documentation. The committee discussion from TA755 noted concerns around the methods used to estimate the effectiveness of BSC, the same concerns are likely to apply here.³ The EAG understands model estimates for BSC come from the unanchored MAIC between ENDEAR and FIREFISH.⁶⁴ The model includes relative effectiveness estimates in the BSC arm for OS, EFS (not on permanent ventilation or dead), and motor milestone improvements. Table 55 reports the relative effectiveness estimates used in the economic model to derive transition probabilities for BSC. The EAG considers that the difference between the 'sitting to standing' odds ratio (OR) and the 'standing to walking' OR may be a typo as this assumption was not reported in the company submission.

Table 55: Relative effectiveness estimates used in the Roche economic model to derive monthly transition probabilities for BSC

BSC	uMAIC	95% CI	95% CI
Event Free Survival (EFS, HR)*	■	■	■
Overall Survival (OS, HR)	■	■	■
Not Sitting to Sitting (OR)	■	■	■
Sitting to Standing (OR)	■	■	■
Standing to Walking (OR)	■	■	■
*EFS = alive and not on permanent ventilation Abbreviations: BSC = best supportive care; uMAIC = unanchored multiple adjusted indirect comparison; CI = confidence interval; HR = hazards ratio; OR = odds ratio			

To compare nusinersen versus risdiplam the company used estimates from the unanchored MAIC using results from ENDEAR and FIREFISH.⁶⁴ Hazard ratios were derived for OS and EFS, whereas effectiveness estimates for motor milestone improvements were presented as odds ratios for HINE-2 endpoints and were transformed to monthly probabilities. Table 56 reports the relative effectiveness estimates used in the economic model to derive transition probabilities for nusinersen.

Table 56: Relative effectiveness estimates used in the Roche economic model to derive monthly transition probabilities for nusinersen

Nusinersen	uMAIC	95% CI	95% CI
Event Free Survival (EFS, HR)	■	■	■
Overall Survival (OS, HR)	■	■	■
Not Sitting to Sitting (OR)	■	■	■
Sitting to Standing (OR)	■	■	■
Standing to Walking (OR)	■	■	■
*EFS = alive and not on permanent ventilation Abbreviations: BSC = best supportive care; EFS = event-free survival; uMAIC = unanchored multiple adjusted indirect comparison; CI = confidence interval; HR = hazards ratio; OR = odds ratio			

For modelling the relative effectiveness of risdiplam versus OA the company used estimates from the unanchored MAIC using results from FIREFISH⁵⁶ and STRIVE-EU^{44,65} The economic model used the hazard ratio of the comparison for EFS, and a MAIC using HINE-2 and BSID-III as clinical endpoints for risdiplam and OA, respectively, to estimate odds ratios for motor milestone improvements and transform them into monthly probabilities. The uncertainty

around motor milestone improvements was not explicitly included in the economic model. Table 57 reports the relative effectiveness estimates used in the economic model to derive transition probabilities for OA.

Table 57: Relative effectiveness estimates used in the Roche economic model to derive monthly transition probabilities for OA

OA	uMAIC	95% CI	95% CI
Event Free Survival (EFS, HR)	■	■	■
Overall Survival (OS, HR)	■	■	■
Not Sitting to Sitting (OR)	■	■	■
Sitting to Standing (OR)	■	■	■
Standing to Walking (OR)	■	■	■
*EFS = alive and not on permanent ventilation Abbreviations: BSC = best supportive care; CI = confidence interval; uMAIC = unanchored multiple adjusted indirect comparison; HR = hazards ratio; OR = odds ratio; OA= onasemnogene abeparvovec			

EAG comment: As detailed in Section 7.2, the EAG's decision problem focused on the comparison between risdiplam and BSC. Due to the lack of evidence comparing these to modes of treatment, the analysis relied on the unanchored MAIC estimates between FIREFISH⁵⁶ and ENDEAR.²⁷

Beyond the changes to the decision problem, the EAG noted several issues with the estimates used for the comparison of risdiplam against other modes of treatment. The OR estimates comparing risdiplam with BSC did not match the OR estimates reported in Ribero et al 2022⁶⁴. As the EAG was not able to corroborate the estimates in the company's base-case analysis, our analysis focused on using the published estimates from Ribero et al 2022 when it was deemed appropriate.⁶⁴

Outside the base-case analysis comparing risdiplam with BSC, the EAG explored scenarios where patients eligible for risdiplam were also eligible for nusinersen, and where patients eligible for risdiplam were also eligible for OA. The estimates of relative effectiveness in the EAG scenario analyses were extracted from Ribero et al 2022⁶⁴ where available.

Where estimates of relative effectiveness were unavailable, the EAG assumed treatment equivalence. This was consistent with the approach taken by the company, however unlike the company the EAG explicitly incorporated uncertainty around the assumption of equivalence. The EAG was also concerned about how uncertainty in the relative effectiveness estimates was handled in the economic model and therefore revised the input methodology to better reflect this uncertainty.

7.3.3.6 Health related quality of life

Same as the presymptomatic model (see section 7.3.2.6)

7.3.3.7 Resource use and costs

Same assumptions as the presymptomatic model (see section 7.3.2.7).

In line with SMPC, the economic model for type 1 SMA patients also assumed that patients < 2 years old require an average monthly dose of 0.2 mg/kg (of bodyweight) until they reach the

age of 2, followed by a monthly dose of 0.25 mg/kg of bodyweight until they reach a bodyweight of 20 kg (approximately [REDACTED] of age predicted in the model). Above a bodyweight of 20 kg patients receive a monthly dose of risdiplam of 5 mg. Trial data and natural history of disease studies were pooled to generate patient weight estimates. Relative dose intensity was assumed to be equal to the FIREFISH part 2 trial at [REDACTED].⁴⁴

EAG comment: The critique to the presymptomatic methods also applies here (see Section 7.3.2.7).

7.3.3.8 Adverse events

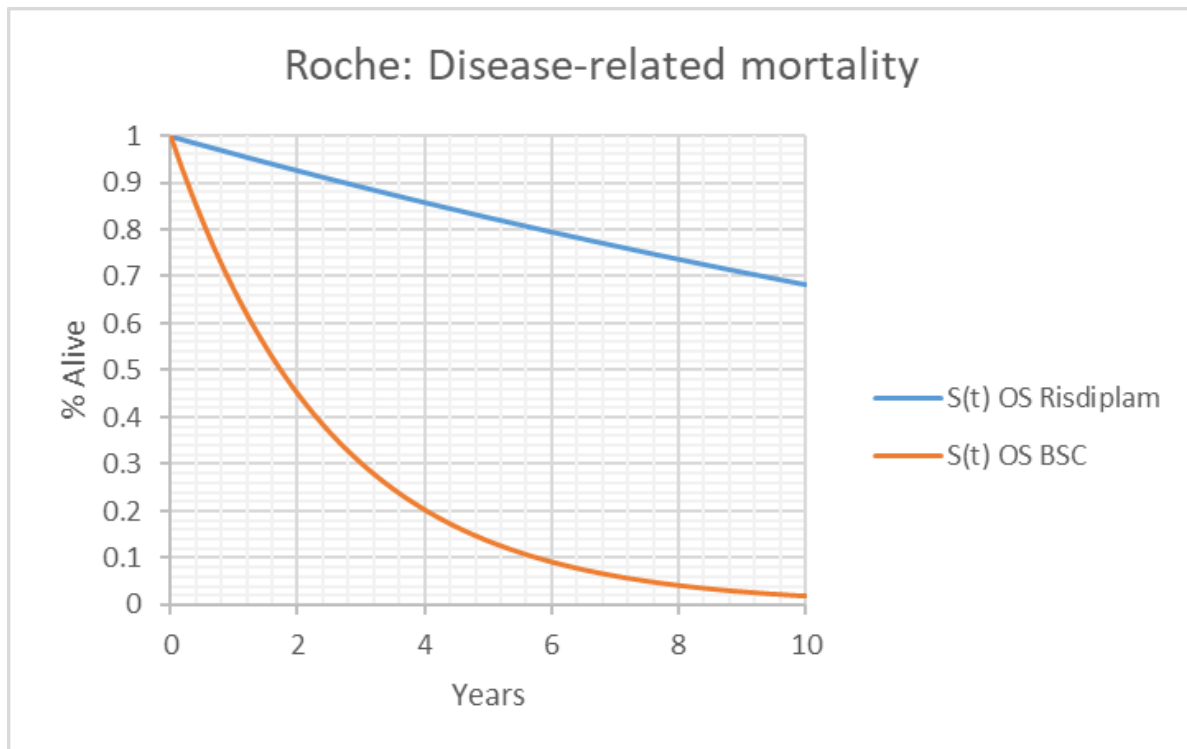
The company did not include the costs associated with adverse events in the model. This was informed by RAINBOWFISH, FIREFISH, and SUNFISH where the incidence was less than 5% of severe treatment-related adverse events.⁴⁴ The economic model did include the impact of non-permanent respiratory support from Wadman et al. 2017,³⁹ severe scoliosis from Winjgaarde et al. 2019,³⁶ and bulbar dysfunction from van der Heul et al. 2019⁷³ as disease-related events across all treatments. Their occurrence depends on motor milestone health-states in the model (i.e. by improving motor milestones disease modifying therapies decrease the occurrences of these events).

EAG comment: The EAG was concerned about double counting disease-related events in patient HRQoL, as the health-state utility values are expected to include the impact of the disease on the general SMA patient population. Moreover, the data used to model their impact on patient HRQoL is not derived from clinical trial data and has not been validated by clinicians; it therefore risks further underestimating the HRQoL values of the patient population. To maintain consistency across economic models, the EAG assumed that the utility values for each motor milestone capture the impact of the disease and disease-related events.

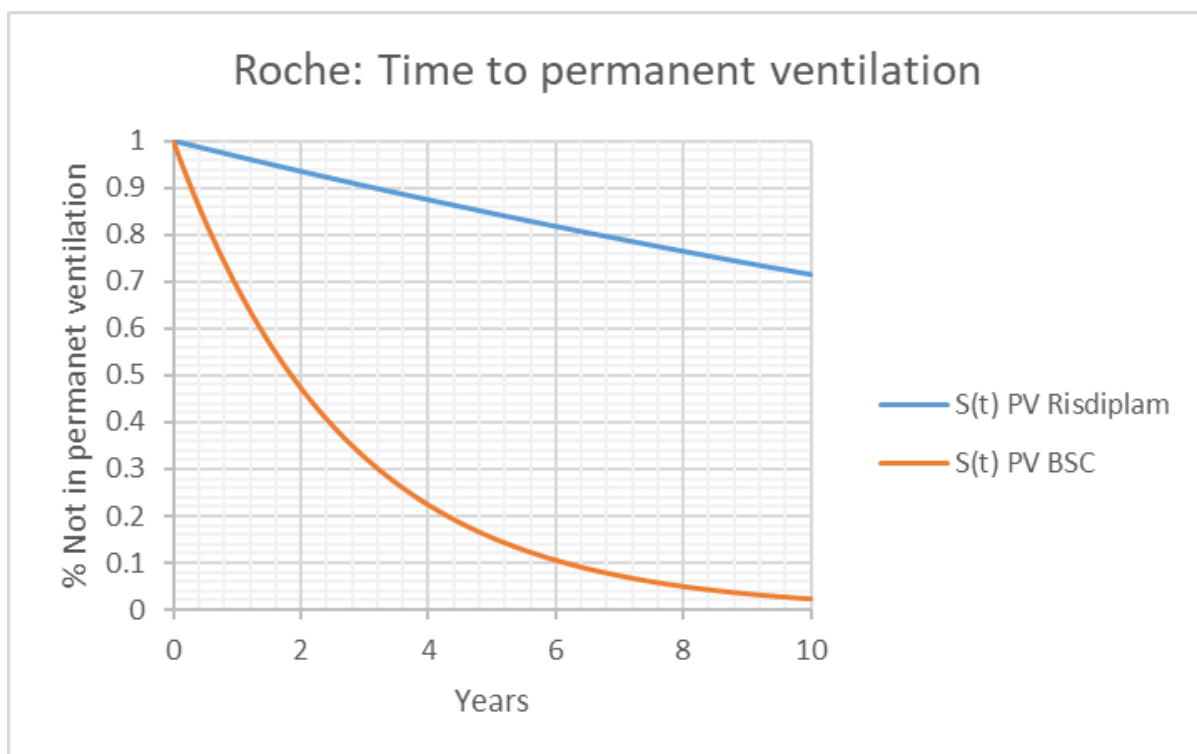
7.3.3.9 Survival

Patient data on time to event for permanent ventilation or death informed EFS in FIREFISH part 1 and 2 over 48 months and was used to inform the risdiplam arm.⁵⁴ The company's approach to calculating time to permanent ventilation involved subtracting the predicted survival curve of mortality from the predicted EFS curve (free from permanent ventilation or death). Survival analysis was performed on time to permanent ventilation or death to fit a parametric survival model. The exponential survival model was chosen based on clinical expert opinion to model the risk of permanent ventilation or death despite being ranked as the lowest statistical fit. The Generalised Gamma curve was reported as having the best statistical fit, yet this curve was also reported as not converging, therefore it was unclear how statistical fit was assessed in the first place.

Overall survival data from FIREFISH part 1 and 2 over 48 months was used to inform the risk of mortality in risdiplam.⁵⁴ The company fitted a parametric survival model to predict survival over the long term. The exponential curve was chosen based on expert opinion despite having a lower statistical fit compared to other parametric models.

Figure 19: Disease-related overall survival for type 1 patients: risdiplam and BSC

Abbreviations: BSC = best supportive care; OS = overall survival

Figure 20: “Free from permanent ventilation” survival for type 1 patients: risdiplam and BSC

Abbreviations: BSC = best supportive care; PV = permanent ventilation

EAG comment: Long-term predictions of overall survival and EFS (free from death or permanent ventilation) for the BSC treatment arm largely reflected the severity of the condition. The EAG had concerns about the potential that longer-term changes in the relative risks of BSC beyond the trial follow-up may not have been captured due to the nature of the data, as FIREFISH was a single-arm trial that relied on an unanchored MAIC to predict the risks of BSC.⁵⁴

The long-term predictions of permanent ventilation derived from the difference in the probability of OS and EFS (free from death or permanent ventilation) meant that if the risk of death was high enough relative to the risk of not being event free, the risk of permanent ventilation would be zero. Acknowledging these limitations stemming from the data available from the clinical trials, the EAG considers the methodological analysis of the evidence to be adequate.

7.3.3.10 Discontinuation

No assumption of treatment-related discontinuation applied for risdiplam and nusinersen, see Section 7.3.2.10 for details and EAG comment.

7.3.3.11 Decision modifier: severity

The company analysed the proportional and absolute shortfall of BSC, and the comparators nusinersen and OA, and applied a severity multiplier of 1.7 to the incremental QALY results across all pairwise comparisons.

EAG comment: In the submission, the company compared risdiplam versus nusinersen, OA, and BSC applying the severity modifier, respectively, to their base-case scenario which also included carer utilities. The EAG considered this an erroneous approach, as the severity modifier should only be based on and applied to patient utilities. The EAG has reported the company results, as well as separate results for informal carers and the severity modifier on patient utilities only.

7.3.3.12 Company's cost-effectiveness results (type 1 SMA)

In the company's base-case scenario analysis including the patient and informal carer quality of life estimates, severity modifiers, and using PAS discount prices for risdiplam against the comparator's list price, [REDACTED] against nusinersen and OA, and it was more effective and more costly compared to BSC. The increase in costs per QALY gained for risdiplam compared to BSC was [REDACTED], higher than NICE's £30,000/QALY threshold. Removing the severity modifier applied to both patient and carer utilities resulted in an ICER of [REDACTED]. Re-applying the severity modifier to patient utilities only resulted in an ICER of [REDACTED].

The probability of risdiplam being cost-effective at a WTP of £30,000/QALY was [REDACTED].

Table 58: Deterministic and probabilistic results for the type 1 population reported in the Roche submission (using risdiplam PAS price)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Deterministic							
Risdiplam	[REDACTED]	13.48	[REDACTED]	-	-	-	-
Nusinersen	[REDACTED]	11.26	[REDACTED]	[REDACTED]	2.22	[REDACTED]	[REDACTED]

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
OA	██████	12.92	██████	██████	0.56	██████	██████
BSC	██████	6.79	██████	██████	6.69	██████	██████
Probabilistic							
Risdiplam	██████		██████				
Nusinersen	██████		██████	██████		██████	██████
OA	██████		██████	██████		██████	██████
BSC	██████		██████	██████		██████	██████
Source: company submission ⁴⁴ Abbreviations: BSC = best supportive care; LY = life year; OA = onasemnogene abeparvovec; QALY = quality-adjusted life year;							

Table 59: Deterministic results using carer utilities without the severity modifier (using risdiplam PAS price)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Deterministic							
Risdiplam	██████	13.48	██████				
Nusinersen	██████	11.26	██████	██████	2.22	██████	██████
OA	██████	12.92	██████	██████	0.56	██████	██████
BSC	██████	6.79	██████	██████	6.69	██████	██████
Source: company submission ⁴⁴ Abbreviations: BSC = best supportive care; LY = life year; OA = onasemnogene abeparvovec; QALY = quality-adjusted life year							

Table 60: Deterministic results using patient utilities only with the severity modifier (using risdiplam PAS price)

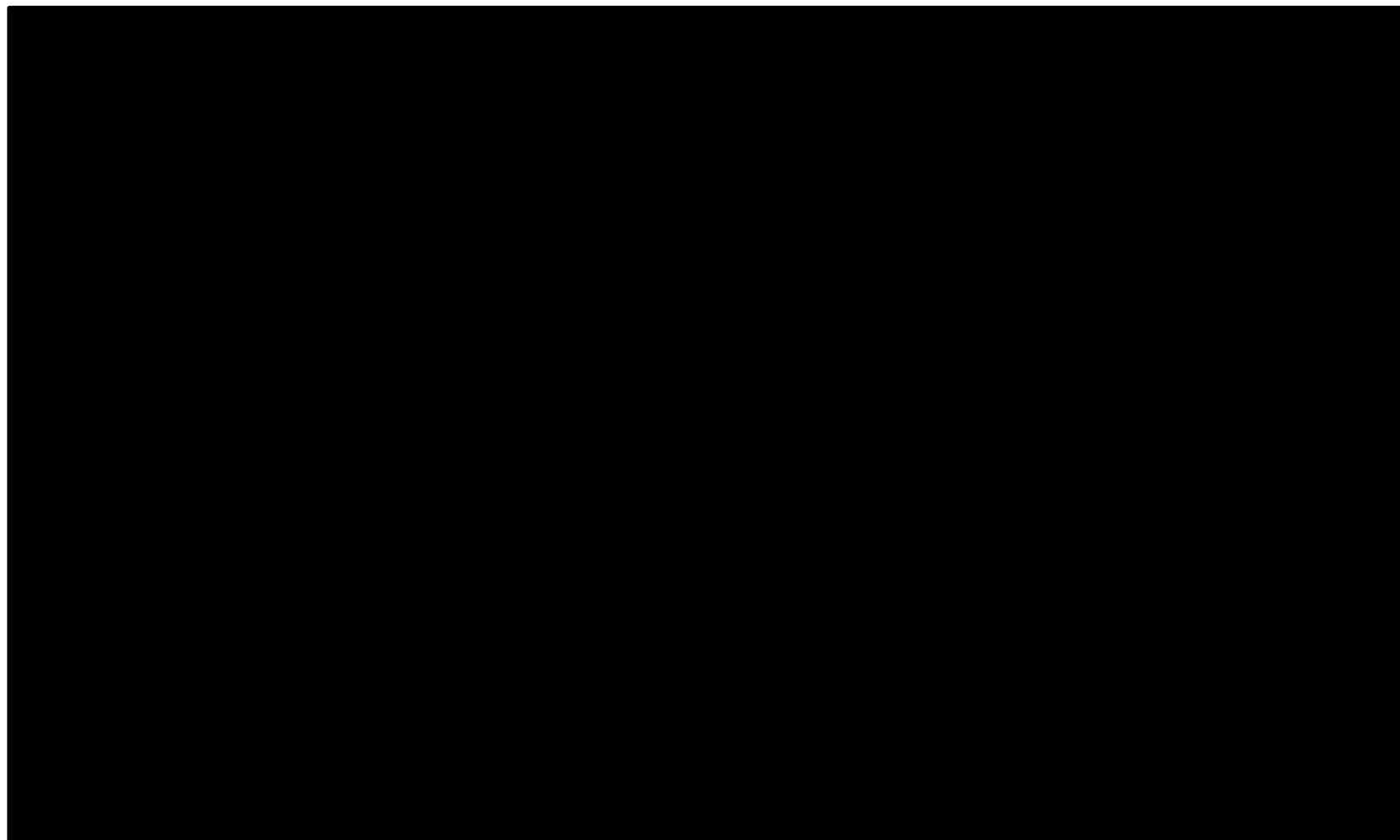
Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Deterministic							
Risdiplam	██████	13.48	██████	-	-	-	-
Nusinersen	██████	11.26	██████	██████	2.22	██████	██████
OA	██████	12.92	██████	██████	0.56	██████	██████
BSC	██████	6.79	██████	██████	6.69	██████	██████
Source: company submission ⁴⁴ Abbreviations: BSC = best supportive care; LY = life year; OA = onasemnogene abeparvovec; QALY = quality-adjusted life year							

7.3.3.12.1 Deterministic sensitivity analysis (type 1)

Risdiplam compared to BSC

The parameters with the most impact on the ICER between risdiplam and BSC were the HR of OS, the HR of EFS, the cost of risdiplam, and the caregiver utility at sitting. The biggest impact on costs came from the cost of risdiplam, and relative effectiveness on OS and EFS. Similarly, the biggest impact on quality of life came from the relative effectiveness on OS and EFS, and carer utility at the “sitting” health-state.

Figure 21: Deterministic sensitivity analysis on incremental QALYs: risdiplam versus BSC (type 1)

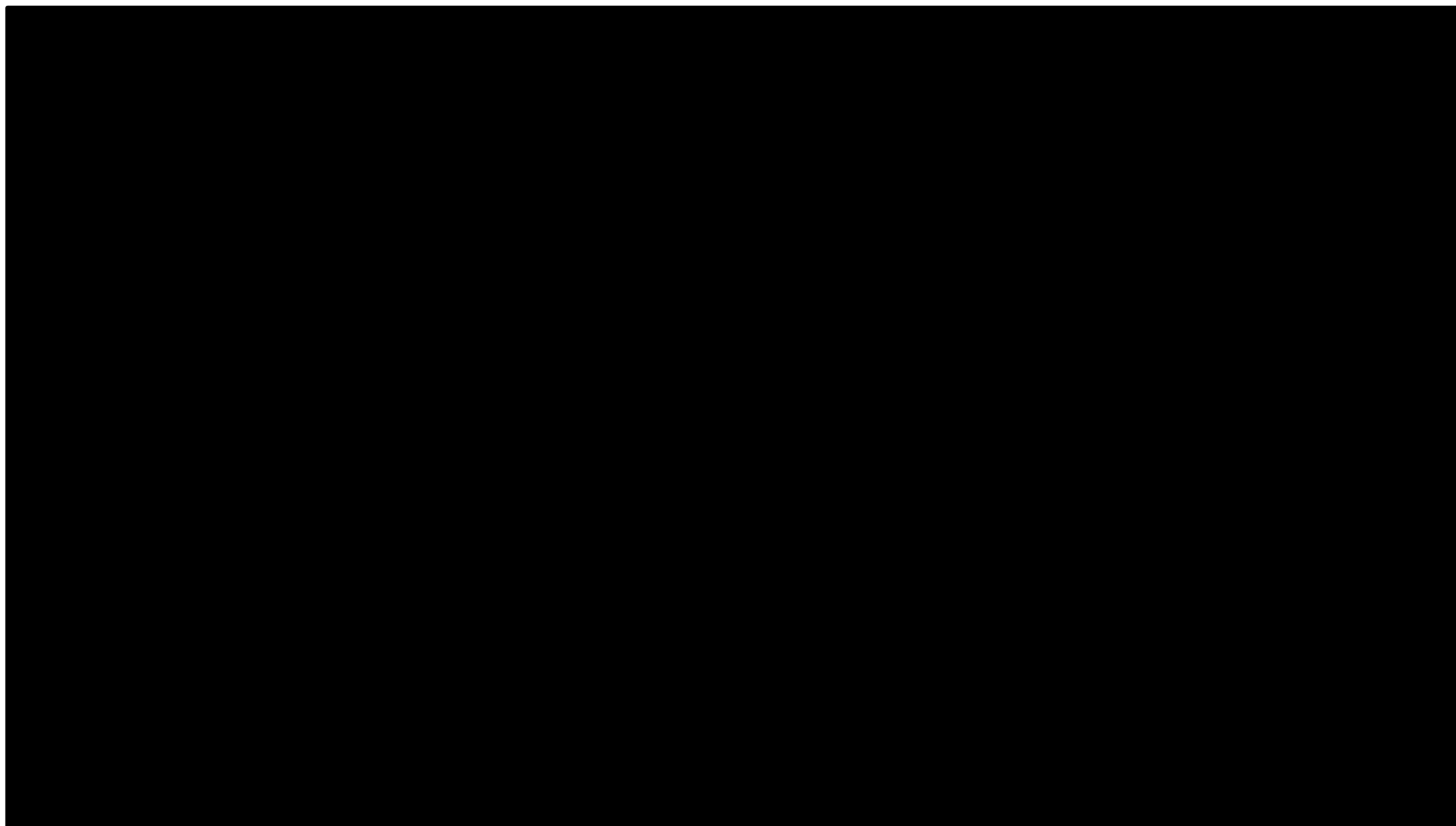


Abbreviations: ICER = incremental cost-effectiveness ratio; HR = hazard ratio; HSUV = health state utility value; OS = overall survival; QALY = quality-adjusted life year; RDI = relative dose intensity

Risdiplam versus nusinersen

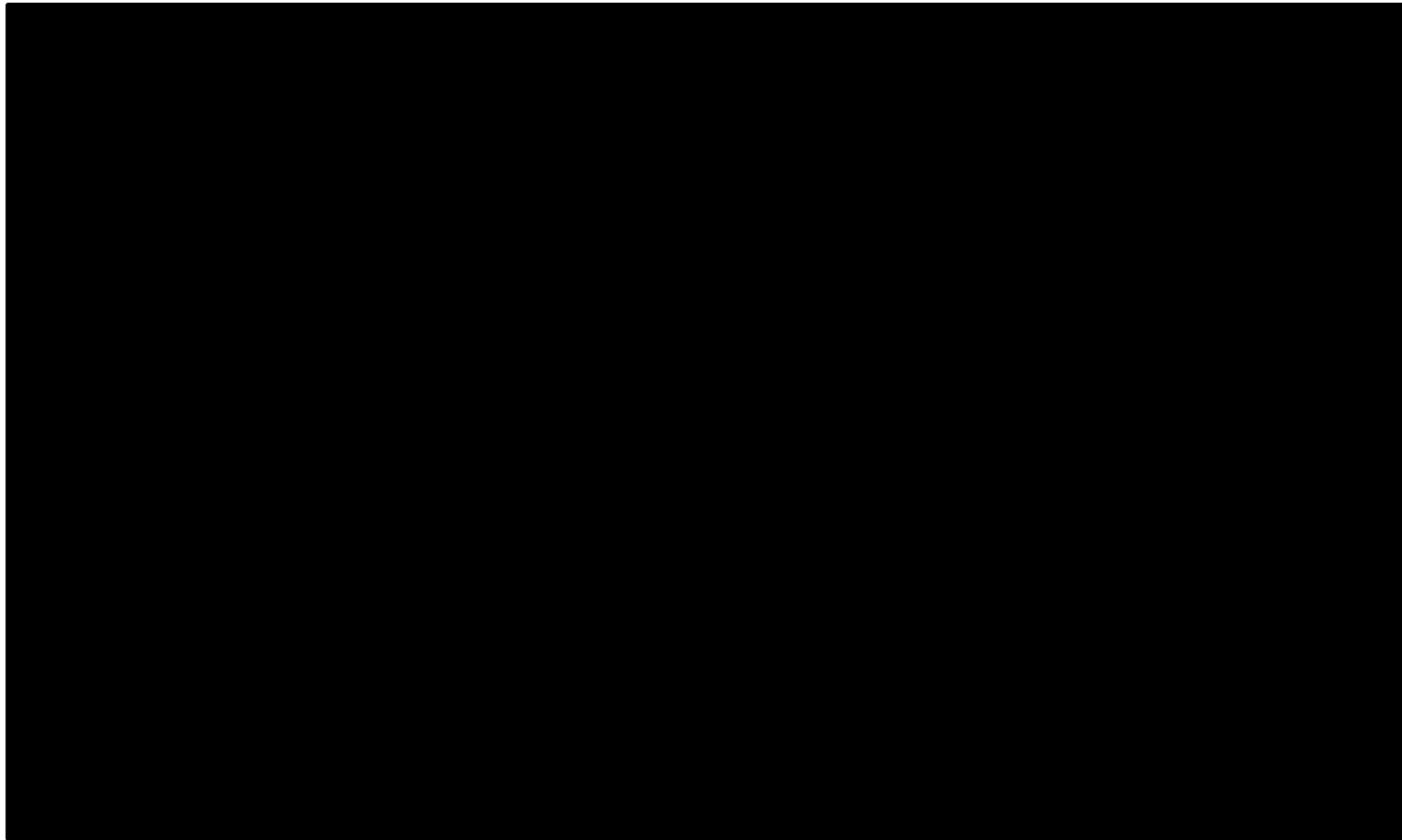
Parameters with the biggest impacts on costs were the drug costs of nusinersen and the cost of risdiplam, as well as the relative effectiveness on OS and EFS. Parameters with the biggest impacts on quality of life were the relative effectiveness on EFA and OS, the utility benefits from risdiplam or nusinersen for the “sitting” health-state.

Figure 22: Deterministic sensitivity analysis on incremental costs: risdiplam versus nusinersen (type 1)



Abbreviations: EFS = event-free survival; HR = hazard ratio; OS = overall survival; RDI = relative dose intensity

Figure 23: Deterministic sensitivity analysis on incremental QALYs: risdiplam versus nusinersen (type 1)

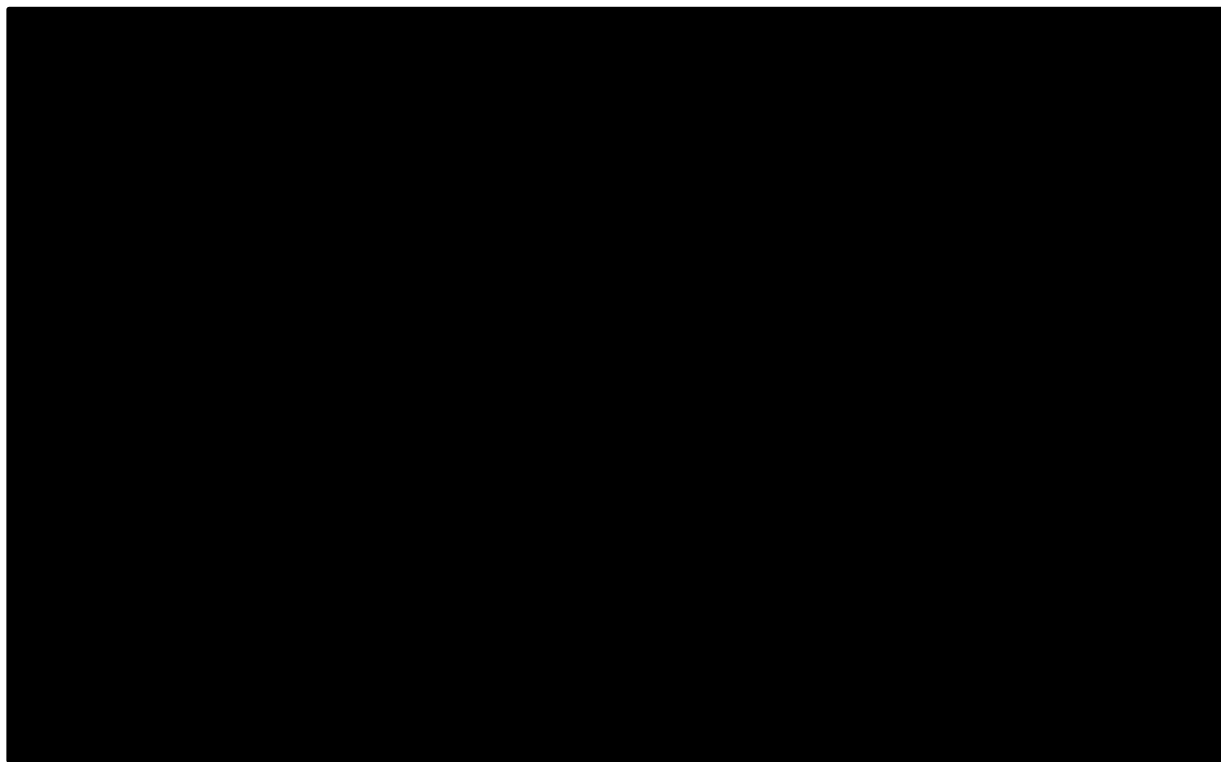


Abbreviations: EFS = event-free survival; HR = hazard ratio; HSUV = health state utility value; OS = overall survival

Risdiplam compared to OA

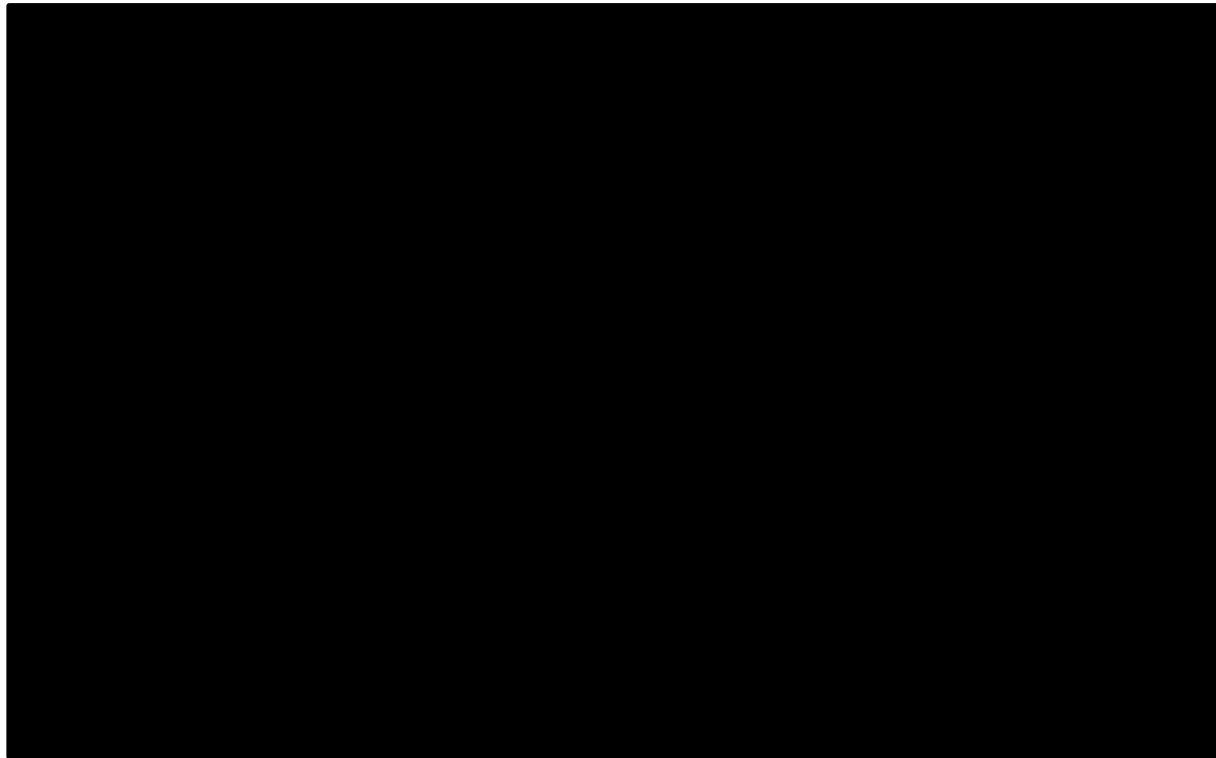
The parameters with the largest impact on costs were the drug costs of OA and risdiplam, respectively, the relative dose intensity of risdiplam, and patient costs at the “sitting” state. For quality-of-life, parameters with the largest impact were relative effectiveness on EFS, and patient utility benefits from risdiplam and OA in the “sitting” states.

Figure 24: Deterministic sensitivity analysis on incremental costs: risdiplam versus OA (type 1)



Abbreviations: EFS = event-free survival; HR = hazard ratio; OA = onasemnogene abeparvovec; RDI = relative dose intensity

Figure 25: Deterministic sensitivity analysis on incremental QALYs: risdiplam versus OA (type 1)



Abbreviations: EFS = event-free survival; HR = hazard ratio; HSUV = health state utility value; OA = onasemnogene abeparvovec; QALY = quality-adjusted life year;

7.3.3.12.2 Company's scenario analysis (type 1)

Risdiplam across all scenarios when compared independently to nusinersen, and to OA. When compared to BSC, scenarios that had the largest impact on the ICER were using the health-state related costs from TA588, using the PV costs from TA588, and using alternative health-state utility values from TA588.²

Table 61: Scenario analyses from Roche submission (type 1)

Scenario	BSC	% ICER change*	Nusinersen	OA
Base case		-		
Efficacy scenarios				
Comparative efficacy vs. OA: Source for OA set to STC STR1VE-US		-		
Risdiplam transition probabilities informed by bootstrapped multi-state model 5				
Source for % scoliosis: based on fixed proportions over time based on FIREFISH				
Source for % respiratory support: on fixed proportions over time based on FIREFISH				
Source for % bulbar dysfunction: on fixed proportions over time based on FIREFISH				
HCRU scenarios				
Alignment with TA588 source for HCRU				
Alignment with TA588 source for HCRU and PV health state costs: 175% increase from the "Not Sitting" health state				
Utility values scenarios				
Source for patient utility values: EQ-5D-3L (NICE ERG TA588) ²				
Source for patient utility values: EQ-5D-Y (Lloyd et al. 2019) ⁶⁷				
Source for caregiver utility values: Roche utility survey (96)				
Source for caregiver utility values: UK Burden of Illness Study ⁴⁴				
Other scenarios				

Scenario	BSC	% ICER change*	Nusinersen	OA
Changing time horizon to 20 years				
Changing time horizon to 40 years				
Inclusion of VAT saving from risdiplam homecare				
Changing baseline characteristics to REACH UK patient population				
Number of carers lowered to 2				
Number of carers increased to 3				
Discount rate for both costs and benefits is lowered to 1.5%				
Discount rate for benefits is lowered to 1.5%, discount rate for costs remains 3.5%				
*Relative to the base-case ICER Abbreviations: ERG = External Review Group; HCRU = health care resource use; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; OA = onasemnogene abeparvovec; UK = United Kingdom; VAT = value added tax				

7.3.4 Type 2 and 3 population

7.3.4.1 Model structure

Type of model: Roche used a Markov model to represent the natural history of type 2/3 5q SMA which was primarily informed by the previous NICE TA755 (see Figure 17).³

7.3.4.1.1 Health states and transitions:

The Markov model was built in Microsoft Excel with five mutually exclusive health states: Four were defined following MFM32 scores as: “not sitting”, “sitting with support”, “sitting unsupported”, “standing (with or without support)”.⁴⁴ The definition of the “walking (with or without support)” health state was derived from the HFMSE scoring measure using the ‘level of independent mobility: highest current level of independent mobility’ as neither the MFM32 nor the HFMSE were able to accurately capture this dimension.⁴⁴ Table 62 presents the model motor milestone-related states with their respective definitions.

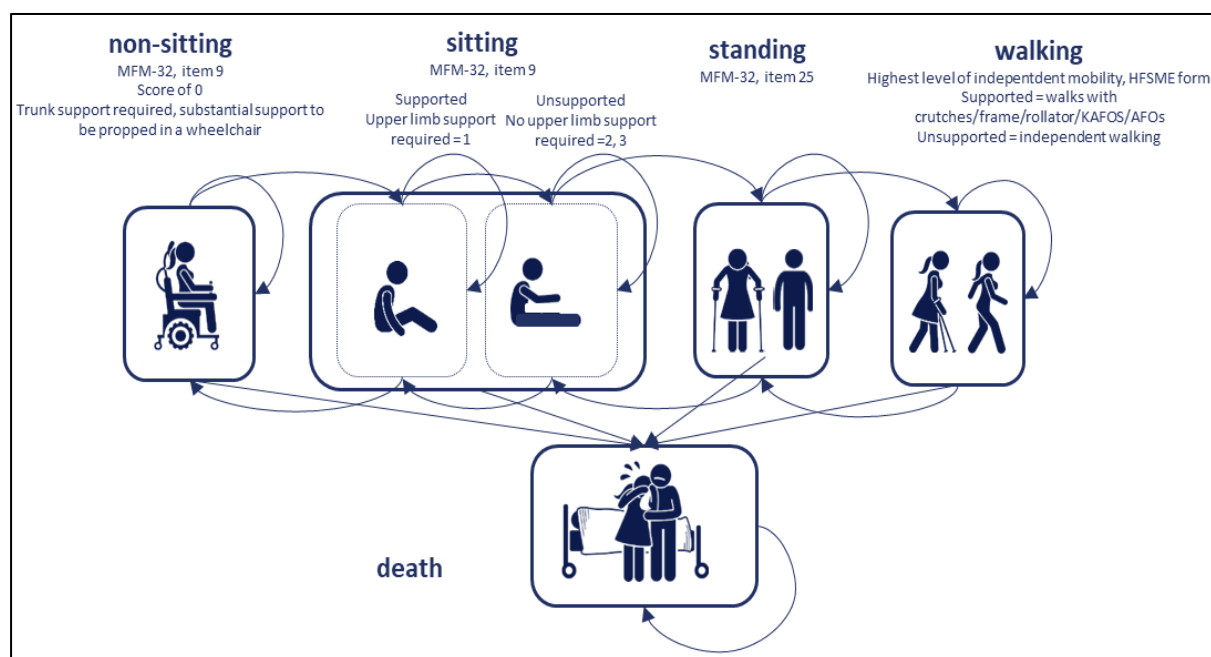
Table 62: Model health state definitions based on MFM-32/HFMSE scores

Health state	MFM-32 item and score
Not sitting	Item 9 (maintain seated position) = 0 (not able to maintain)
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)

Health state	MFM-32 item and score
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 (with or without support)	HFMSE 'level of independent mobility: highest current level of independent mobility'
Abbreviations: HFMSE = Hammersmith Functional Motor Scale Expanded; MFM=32 = 32-item Motor Function Measure	

Patients start the model distributed across the motor milestone states based on proportions from the SUNFISH trial,⁴⁷ and it was assumed that each model cycle with a duration of one month, patients could either maintain their motor milestone state, improve to a higher motor milestone or lose mobility and decline to a previous motor milestone. Death was the absorbing state to which patients could move into from any state at any cycle. The arrows in the Figure 26 indicate the direction of transitions across model health states.

Figure 26: Model structure for the later-onset SMA population used by Roche (type 2/3)



Source: company submission⁴⁴

Abbreviations: AFO: ankle-foot orthosis; HFMSE: Hammersmith Functional Motor Scale Expanded; KAFOS: knee-ankle-foot-orthosis; MFM32: 32 Item Motor Function Measure

Transition probabilities for the risdiplam arm were based on a subgroup population of the SUNFISH trial (excluding patients from Asia), over the 60-month trial follow-up.⁵³ This subgroup was selected due to concerns from clinical experts around differences in standard of care from the UK clinical practice. Data from the placebo arm of SUNFISH were available for a 52-week follow-up,⁴⁷ a subgroup of this data excluding patients from Asia was used to calculate the motor milestone transition probabilities for BSC. Table 63 presents the motor milestone transitions from risdiplam, and Table 64 presents the motor milestone transitions for BSC. Figure 27 and Figure 28 present the modelled motor-milestone predictions based on the probabilities for risdiplam and BSC, respectively.

Table 63: Transition probabilities for risdiplam (type 2/3 model)

From\To	Not Sitting	Sitting (supported)	Sitting (unsupported)	Standing	Walking
Not Sitting	■	■			
Sitting (supported)	■	■	■		
Sitting (unsupp)		■	■	■	
Standing			■	■	■
Walking				■	■

Table 64: Transition probabilities for BSC (type 2/3 model)

From\To	Not Sitting	Sitting (supported)	Sitting (unsupported)	Standing	Walking
Not Sitting	■	■			
Sitting (supported)	■	■	■		
Sitting (unsupp)		■	■	■	
Standing			■	■	■
Walking				■	■

Abbreviations: BSC = best supportive care

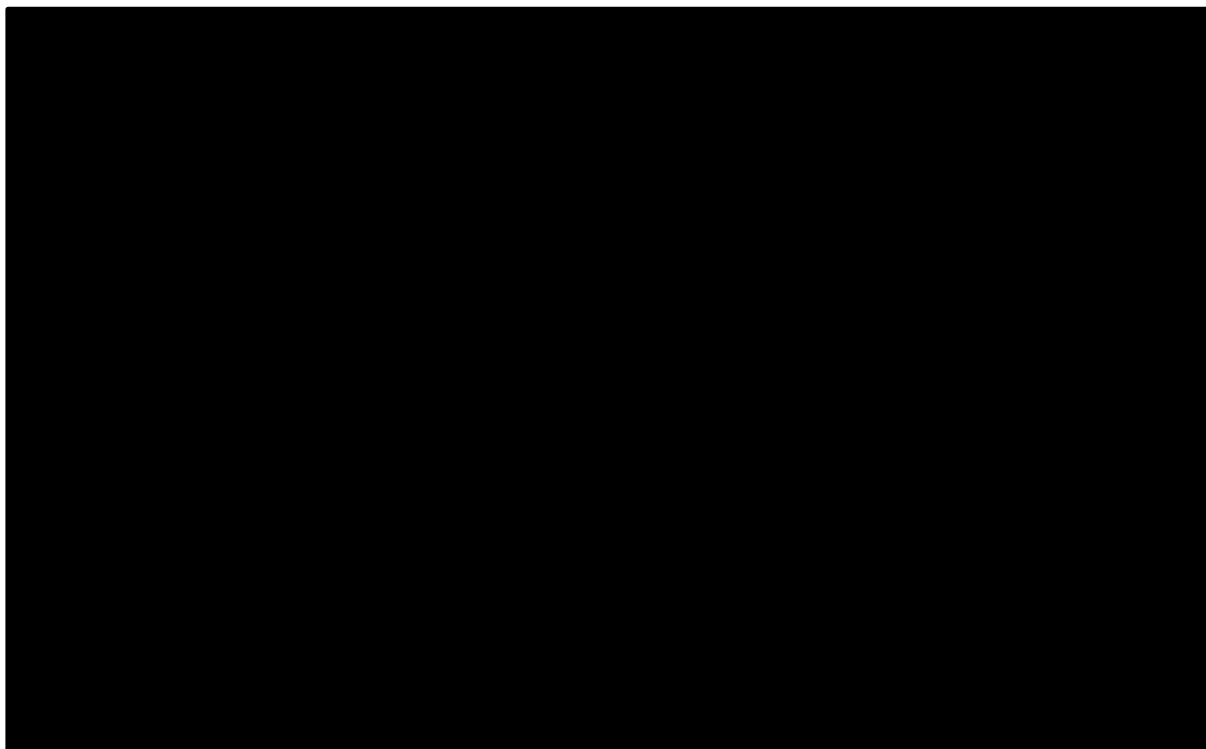
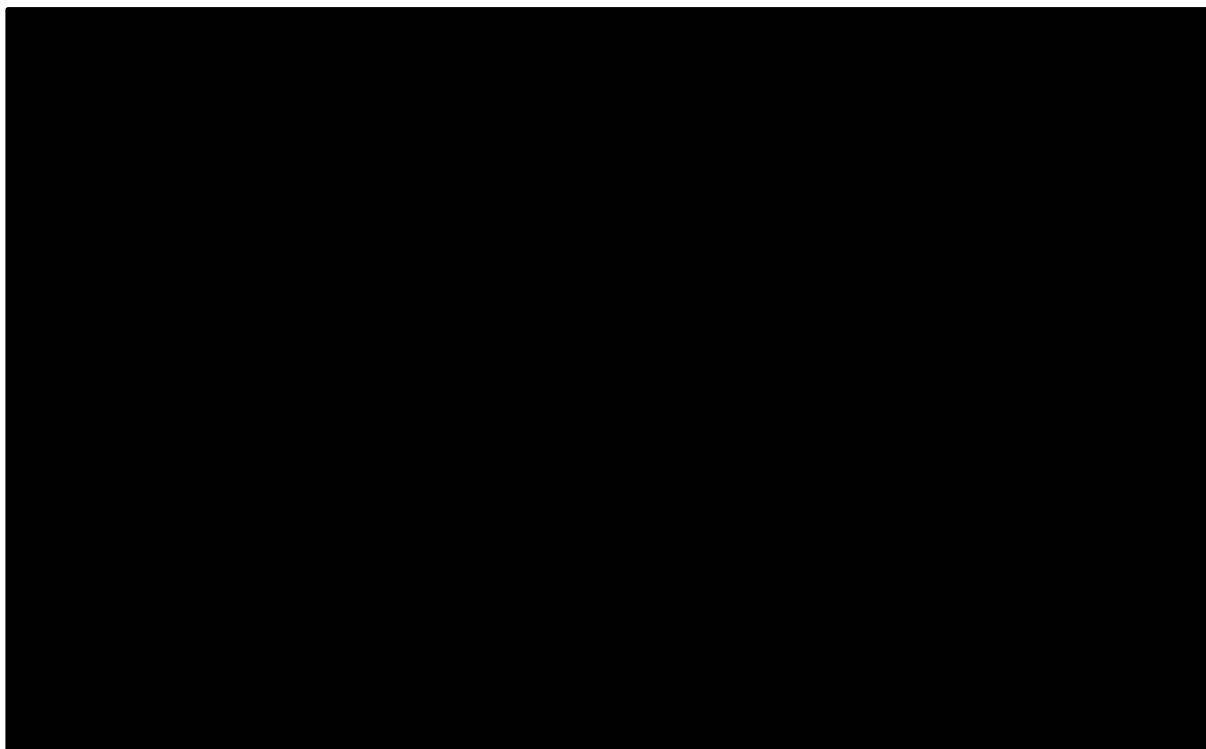
Figure 27: Modelled motor-milestone predictions for risdiplam over four years (type 2/3)

Figure 28: Modelled motor-milestone predictions for risdiplam over one year (type 2/3)

Abbreviations: BSC = best supportive care

After the 60-month SUNFISH follow-up data for risdiplam,⁵³ the model assumes that patients reach long-term stability and can only improve or maintain their motor milestones, the equivalent long-term assumption is applied to nusinersen. BSC patients are assumed to either maintain or decline their motor-milestones after 24 months.

EAG comment: The EAG considered the model structure to represent an adequate picture of the primary outcome trial data available, while also acknowledging the existence of further mobility improvements in SMA that may not have been captured by the motor milestone-based health states as defined in the economic model, but that will have an impact on patient health-related quality of life and were not being captured due to gaps in the quantitative evidence.

Although the EAG understands the pragmatic reasons to exclude the Asian population from the data, it was unclear how much this affected the baseline characteristics of the subgroup dataset as the EAG was unable to corroborate this from the documents submitted. Moreover, although the approach to fit trial data to the Markov chain likely followed a similar procedure as with the type 1 data (based on information criteria coefficients), the EAG could not access this information or the visual plots for type 2/3.

Finally, as with the presymptomatic and type 1 model, long-term assumptions of maintenance of motor milestones under treatment were of concern to the EAG, as clinical feedback suggested that long-term risks of motor decline may be present even during treatment.

The EAG decided to align the approach to long-term effectiveness in the Roche model with that of the Biogen model to maintain consistency in the assumptions of disease progression over the long-term. This meant that the effect of disease modifying therapies was not lifelong, instead DMTs allow patients to reach motor milestone improvements for a duration of time

that matches the available clinical trial evidence. After this period, patients either maintain their motor milestones or are at risk of losing them over the long-term. For risdiplam the EAG assumed 96 months of motor milestone improvement using SUNFISH trial data for transitions.

Patients receiving BSC were assumed to gain improvements in motor milestones over the first 12 months based using SUNFISH placebo data for transitions. After 12 months the rate of motor milestone decline corresponds to the natural history of SMA disease reported by Wadman et al. 2018.³⁹ The relative rate of motor milestone decline for risdiplam was extracted from Oskoui et al. 2023,⁴⁸ which reports that after 2-years of SUNFISH data 58% of risdiplam patients showed stabilisation of motor milestones from MFM-32 scores.

7.3.4.2 Population

The population modelled in the type 2/3 model reflected the ITT patient characteristics of the global population in SUNFISH presented in Table 65.

Table 65: Type 2/3 SMA patient characteristics in the Roche model

Baseline characteristics	Value
Mean start age, years	10
Female (SE)	50.6%
SMA type	
Type 2	71.1%
Type 3	28.9%
Motor milestones	
Not sitting	0%
Sitting (supported)	13%
Sitting (unsupported)	74%
Standing	6%
Walking	7%

7.3.4.3 Interventions and comparators

The type 2/3 SMA model compared risdiplam against nusinersen and BSC in a population with the characteristics like those reported above in section 7.3.4.2.

Intervention: Same as the presymptomatic model (see Section 7.3.2.3).

Comparators: The company modelled nusinersen and BSC as the comparators for type 2/3 SMA populations.

EAG comment: In line with the critique of the clinical evidence and the limitations in the comparative effectiveness analysis, the base-case economic analysis by the EAG focused on comparing risdiplam with BSC.

7.3.4.4 Perspective, time horizon and discounting

The analysis was conducted from the perspective of the NHS and Personal Social Services (taking account of costs directly related to the medical treatment of SMA patients, and the quality of life of SMA patients and their carers) and with a time horizon of [REDACTED] (considered to cover the lifetime) in the base case. The costs and benefits were discounted at annual rate of 3.5% in accordance with the NICE methods guidelines NICE methods guidelines.⁴⁰

EAG comment: To fully capture the impact of the disease and the interventions across time, the EAG considers a lifetime horizon covering 90 years to be more appropriate but that this may have little impact on the results.

7.3.4.5 Treatment effectiveness and extrapolation

As detailed above, relative effectiveness in motor milestone changes between risdiplam and BSC were informed by the SUNFISH trial data excluding the patient population from Asia to account for differences in standard of care. The risdiplam arm had a follow-up of 60 months (5 years) while the follow-up for the placebo arm informing BSC had a follow-up of 52 weeks (1 year).⁴⁷

An unanchored MAIC was used to compare RULM scores for risdiplam from the SUNFISH trial with RULM score for nusinersen from the CHERISH trial and present them as odds ratios (ORs). Although the company reported high uncertainties around the estimated results from the MAIC, these were used to estimate the relative effectiveness between risdiplam and nusinersen in the economic model. The economic model assumes a monthly relative risk of nusinersen versus risdiplam for improving to a higher motor milestone of [REDACTED] applied to the probability of improving in all health states except “walking”. Crucially, uncertainty around this estimate is not explored, instead, the model only explores uncertainty around transition probabilities with standard errors based on mean values.

EAG comment: As detailed previously, the base-case analysis conducted by the EAG focused on the comparison between risdiplam and BSC given the gaps in high-quality evidence comparing both drugs. The EAG considered the evidence available comparing risdiplam and nusinersen as a scenario analysis caveated by the limitations in the data. This comparison also focused on the relative effectiveness available in a publication by Ribero et al. 2022,⁶⁴ and explored the uncertainty around the relative effectiveness estimate given the published evidence, in addition to uncertainty around transition probabilities. The model also assumes that disease-modifying therapies do not remove the risk of long-term motor milestone decline, therefore the same assumptions of long-term decline were applied between risdiplam and nusinersen.

7.3.4.6 Health related quality of life

The company collected EQ-5D-5L data from the ITT population in the SUNFISH part 2 trial.⁴⁷ These data were used to derive utility estimates, and were presented to a group of clinical experts, along with utility values from a vignette study by Lloyd et al. 2019,⁶⁷ and utility values preferred by the EAG team appraising TA588.² The company base-case used estimates from Lloyd et al. 2019 due to them being preferred by clinical experts and explored the alternative utilities in its scenario analysis.⁶⁷ Table 66 reports the patient utility estimates used in the economic model.

Table 66: Utility values used in the Roche type 2/3 economic model

Base-case utility values			Utilities from TA588 ²		Utilities from SUNSHINE part 2	
Model state	Mean	Source	Mean	Source	Mean	Source
Not sitting	-0.17	Based on Lloyd et al. ⁶⁷	0.2	TA588 ²	[REDACTED]	SUNSHINE part 2 internal data
Sitting (supported)	0.04		0.4		[REDACTED]	
Sitting (unsupported)	0.04		0.5		[REDACTED]	

Base-case utility values			Utilities from TA588 ²		Utilities from SUNSHINE part 2	
Model state	Mean	Source	Mean	Source	Mean	Source
Standing	0.56		0.7			
Walking	0.56		0.85			
Disutilities						
Bulbar function	-0.17		-		-	
Severe scoliosis	-		-			
Respiratory support	-		-			
Age ≥ 12 years old	-		-			
Abbreviations: TA = technology appraisal						

As with the Roche presymptomatic and type 1 models, the type 2/3 model combined health-related quality of life estimates from patients and informal carers. The company base-case used estimates from TA755³ and explored alternative utility estimates from a burden of illness study and a utility survey both conducted by Roche.⁴⁴ Table 67 presents the informal carer utilities used in the company model. The model assumed an average of 2.2 carers per patient across all states except the “not sitting” state, where it assumed an average of 3 carers.

Table 67: Informal carer utilities used in the economic model

Base-case carer utilities			Scenario 1		Scenario 2	
Model state	Mean	Source	Mean	Source	Mean	Source
Not sitting	0.70	TA755 ³	0.75	Roche Bol study ⁴⁴	0.40	Roche utility survey study ⁴⁴
Sitting (supported)	0.77		0.74		0.40	
Sitting (unsupported)	0.84		0.74		0.66	
Standing	0.92		0.72		0.87	
Walking	0.92		0.75		0.87	
Abbreviations: TA = technology appraisal						

The economic model also included an increase in patient utility from receiving a disease-modifying therapy of 0.2 in the “not sitting”, “sitting (supported)”, and “sitting (unsupported)” health states. Similarly, an increase in carer utility of 0.05 was assumed for the same health states.

EAG comment: As with the previous models, the EAG recognises the challenges around methodological approaches for collecting data from young children in this patient population. Due to concerns around face validity of patient utility in this area in previous appraisals (TA588 and TA755^{2,3}) the EAG decided to adopt the approach of the most recently published appraisal in this area, assessing OA in presymptomatic patients (HST24¹⁶), aiming to reach a degree of consistency across economic models.

The EAG was also concerned about the presence of negative utility values in some of the scenarios and have thus adopted an approach where negative utility health-states are assumed to be equivalent to the death state. For further details see the discussion in Section 7.3.2.6.

Regarding the direct impact of disease-modifying therapies, the EAG has assumed these provide an increment of 10% above the mean utility across all health-states, to make our analysis consistent across both company submissions.

The EAG was concerned about the approach for combining both patient and informal carer quality of life in the base-case analysis. The data on informal carer utility was not the result of data collection in the clinical trials, and it was difficult to ratify its validity beyond clinical expert opinion. Moreover, as the critique from the Biogen submission showed, there was a lack of a standardised methodology to include carer quality of life.

The EAG understands the importance of the perspective of informal carers in SMA and the value of including the impact on informal carers in this appraisal. For transparency and clarity in our analyses the EAG focused its base-case analysis exclusively on patient quality of life. An additional scenario analysis was presented including treatment impacts on patient and informal carer quality of life with the aim of exploring the potential impact of treatment on informal carers.

Regarding the values of informal carer utilities, the EAG noted discrepancies between values used from Lloyd et al. 2019 in this population,⁶⁷ and the models in the presymptomatic and type 1 population, and thus strove to make this consistent across all populations.⁶⁷

7.3.4.7 Resource use and costs

Risdiplam resource use: Drug list price and confidential price assumptions, as well as delivery costs were consistent with Section 7.3.2.7. Relative dose intensity was assumed at [REDACTED] based on data part 2 of the SUNFISH trial. Furthermore, since the patient starting age in the model was 10 years, patients were expected to have reached a bodyweight above 20 kg and thus all patients received a regular monthly dose of risdiplam of 5 mg.

Comparator interventions resource use: The same assumptions around drug costs and delivery for nusinersen in the presymptomatic and type 1 model were applied in the type 2/3 model. For more details see Section 7.3.2.7.

Health-state related resource use: Roche reported the results of its own Delphi panel study collecting expert opinion on quantitative estimates for health-care resource use (HCRU) related to the management of SMA type 1 and type 2/3.⁴⁴ Results showed that resource use was high in SMA patients, particularly regarding disease-related healthcare visits, surgeries, and procedures. Costs from NHS reference values were used to derive monthly costs for each motor milestone-related health state. Resource use values from TA588 were used as a scenario analysis.² Table 68 reports the health state related costs used on the Roche economic model for patients with type 2/3 SMA.

Table 68: Health state-related costs in the Roche type 2/3 model

Costs per cycle: base-case				Costs per cycle from TA588
Health state	Paediatric patient	Adult patient	One-off costs	Paediatric and adult
Unable to sit	£1,581	£697	£15,586	£13,284
Sitting with support	£1,315	£521	£9,456	£13,284

Costs per cycle: base-case				Costs per cycle from TA588
Health state	Paediatric patient	Adult patient	One-off costs	Paediatric and adult
Sitting without support	£1,315	£521	£9,456	£9,704
Standing	£660	£189	£2,372	£1,951
Walking	£222	£121	£715	£1,951
Source: company submission ⁴⁴ Abbreviations: TA = technology appraisal				

7.3.4.8 Adverse events

The company did not include the costs associated with adverse events in the model. This was informed by RAINBOWFISH⁵⁷, FIREFISH,⁵⁶ and SUNFISH,⁵³ where the incidence of treatment-related severe adverse events was fewer than 5%. The economic model did include the impact of non-permanent respiratory support, severe scoliosis, and bulbar dysfunction as disease-related events across all treatments using data from an SMA natural history study conducted by Roche.⁴⁴ Their occurrence depends on motor milestone health-states in the model (i.e. by improving motor milestones disease modifying therapies decrease the occurrences of these events).

EAG comment: The EAG was concerned about double counting disease-related events in patient HRQoL, as the health-state utility values are expected to include the impact of the disease on the general SMA patient population. Moreover, the data used to model their impact on patient HRQoL is not derived from clinical trial data and have not been validated by clinicians, and therefore risks further underestimating the HRQoL values of the patient population. To maintain consistency across economic models, the EAG assumed that the utility values for each motor milestone capture the impact of the disease and disease-related events. The EAG explored the impact of adding an additional disutility for bulbar dysfunction based on SUNFISH part 2 data and Lloyd et al 2019 in the scenario analysis.^{47,67}

7.3.4.9 Survival

As with the CHERISH trial for nusinersen,²⁸ data from part 2 in the SUNFISH trial lacked sufficient events to perform a survival analysis that compared survival outcomes between treatment arms.⁵³ Instead, Roche used different assumptions around mortality for type 2 and for type 3 patients respectively.

For type 2 patients, the company selected six studies identified from their systematic review and digitised the Kaplan-Meier curves to create a pooled pseudo-individual patient dataset.⁴⁴ Survival analysis was conducted, and parametric survival functions were fitted to the pooled pseudo-IPD data, with the Gompertz distribution considered the most appropriate according to the goodness of fit statistics and clinical experts' feedback. However, the company explored the Weibull distribution in a scenario analysis. These survival probabilities were applied to Type 2 patients in the "not sitting", "sitting (supported)", and "sitting (unsupported)" health states in the model.

For type 3 patients, the company took evidence from the literature⁷⁴ and assumed overall survival similar to that of the general population taken from Office for National Statistics (ONS) for England.⁴² In addition, in line with the previous NICE technology appraisals and clinical

expert opinion, the company assumed that type 2 patients who reach advanced motor milestone of standing or walking, also had a survival equivalent to that of the general population. The economic model also assumed a 0.75 hazard ratio reducing the risk of mortality for disease-modifying therapies compared to BSC.

EAG Comment: The EAG acknowledges the existence of gaps in the data from the clinical trials in SMA types 2 and 3 regarding patient overall survival. Nonetheless, the EAG was not able to find published evidence backing the 0.75 hazard ratio in the overall risk of death for patients receiving DMTs and was unable to assess the uncertainty around this parameter. The EAG acknowledges that disease-modifying therapies may impact survival, yet the primary role of treatment for type 2 and type 3 patients is on improving health-related quality of life through improvements in mobility and the avoidance of disease-related adverse events, therefore the EAG did not assume a 0.75 relative probability of survival for patients receiving BSC.

In order to maintain consistency across the submissions in this disease area and considering the current gaps in the evidence, the EAG adopted the approach used in the latest submission to NICE for SMA (HST24¹⁶) and assumed that patients in the “not sitting”, “sitting (supported)”, and “sitting (unsupported)” faced a higher mortality risk, based on HST24,¹⁶ to reflect the severity of the condition.¹⁶ Patients at the “standing” and “walking” health states were assumed to follow the mortality of the general UK population, therefore therapies had the potential of impacting survival by decreasing the severity of the condition. The approach to survival used by the Roche base-case was explored as a scenario analysis.

7.3.4.10 Discontinuation

No assumption of treatment-related discontinuation was applied for risdiplam and nusinersen; see section 7.3.2.10 for details and EAG comment.

7.3.4.11 Decision modifier: Severity

The company analysed the proportional and absolute shortfall of BSC, and nusinersen separately, and applied a severity multiplier of 1.7 to the incremental QALY results across all pairwise comparisons.

EAG comment: In the submission, the company compared risdiplam versus nusinersen, and BSC applying the severity modifier, respectively, to their base-case scenario which included carer utilities. This was considered an erroneous approach, as the severity modifier should only be based on and applied to patient utilities. The EAG has reported the company results, as well as separate results for informal carers and the severity modifier on patient utilities only.

7.3.4.12 Company's cost-effectiveness results (types 2 and 3)

In the company's base-case scenario analysis including the patient and informal carer quality of life estimates, severity modifiers, and using PAS discount prices for risdiplam against the comparator's list price, risdiplam was [REDACTED] against nusinersen, and it was more effective and more costly compared to BSC. The increase in costs per QALY gained for risdiplam compared to BSC was [REDACTED] higher than NICE's £20,000/QALY threshold. Correcting by removing the severity modifier from patient and carer utility data led to an ICER of [REDACTED]. Applying the severity modifier exclusively to patient utilities led to an ICER of [REDACTED].

The probability of risdiplam being cost-effective at a WTP of £30,000/QALY was [REDACTED].

Table 69: Deterministic and probabilistic results for the type 2 and 3 population reported in the Roche submission (using risdiplam PAS price)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Deterministic							
Risdiplam	██████	21.63	████	-	-	-	-
Nusinersen	██████	21.51	████	██████	0.13	████	██████████
BSC	██████	20.29	████	██████	1.34	████	██████
Probabilistic							
Risdiplam	██████		████				
Nusinersen	██████		████	██████		████	██████████
BSC	██████		████	██████		████	██████
Source: company submission ⁴⁴ Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year							

Table 70: Deterministic results using carer utilities without the severity modifier (using risdiplam PAS price)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Deterministic							
Risdiplam	██████	21.59	████				
Nusinersen	██████	21.46	████	██████	0.12	████	██████████
BSC	██████	20.29	████	██████	1.30	████	██████
Source: company submission ⁴⁴ Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year							

Table 71: Deterministic results using patient utilities only with the severity modifier (using risdiplam PAS price)

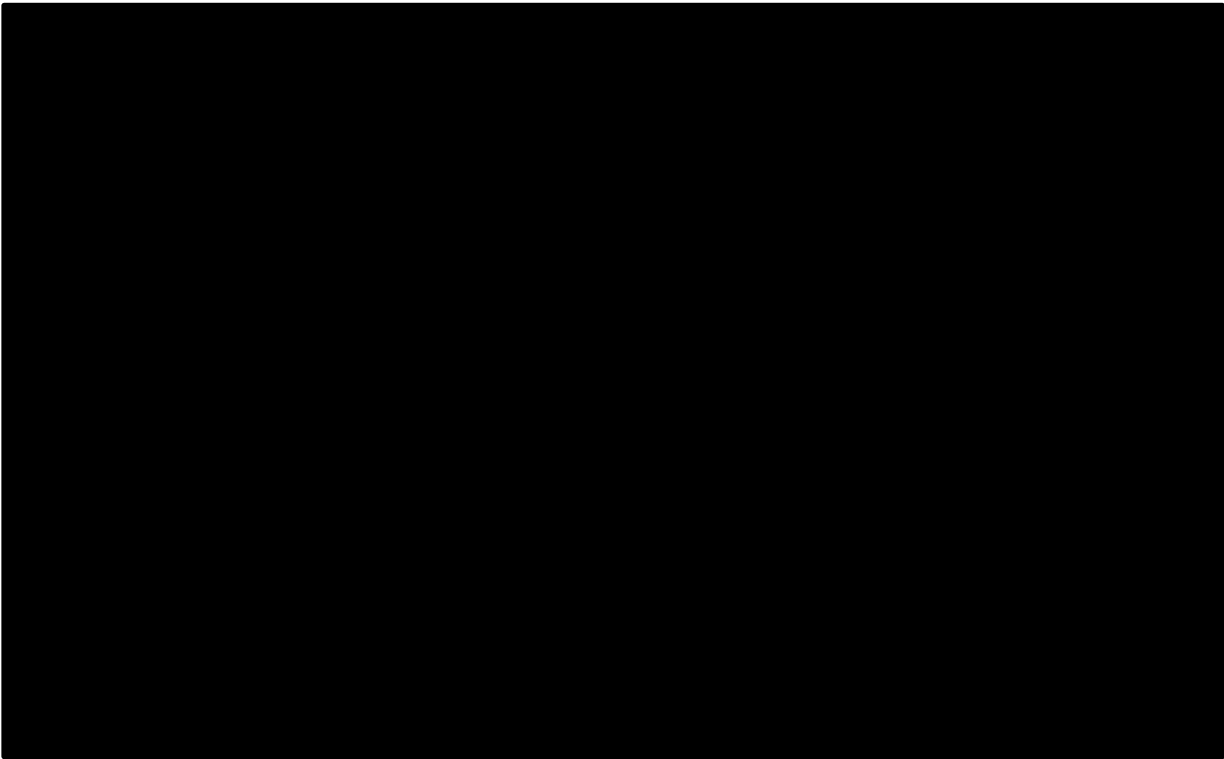
Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Deterministic							
Risdiplam	██████	21.59	████	-	-	-	-
Nusinersen	██████	21.46	████	██████	0.12	████	██████████
BSC	██████	20.29	████	██████	1.30	████	██████
Source: company submission ⁴⁴ Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year							

7.3.4.12.1 Deterministic sensitivity analysis (types 2 and 3)

Risdiplam compared to BSC

The parameters with the most impact on the ICER between risdiplam and BSC were carer utilities for “sitting without support”, the cost of risdiplam, caregiver utilities a “not sitting” and risdiplam treatment benefit at “sitting without support”. For costs those with the greatest impact were risdiplam costs, the proportion of type 2 relative to type 3, and HR of mortality for risdiplam versus BSC. For quality of life this was caregiver utility for “sitting without support” and “not sitting”, and risdiplam treatment benefit at “sitting without support”.

Figure 29: Deterministic sensitivity analysis on the ICER: risdiplam versus BSC (type 2/3)



Abbreviations: BSC = best supportive care; HSUV = health state utility value; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Risdiplam versus nusinersen

Parameters with the biggest impacts on costs were the drug costs of nusinersen and the cost of risdiplam, as well as the HR for mortality for nusinersen and the percentage of type 2 over type 3 patients. Parameters with the biggest impacts on quality of life were treatment-related benefits for risdiplam and nusinersen on patient and carer utilities for “sitting without support” and “not sitting”.

Figure 30: Deterministic sensitivity analysis on incremental costs: risdiplam versus nusinersen (type 2/3)

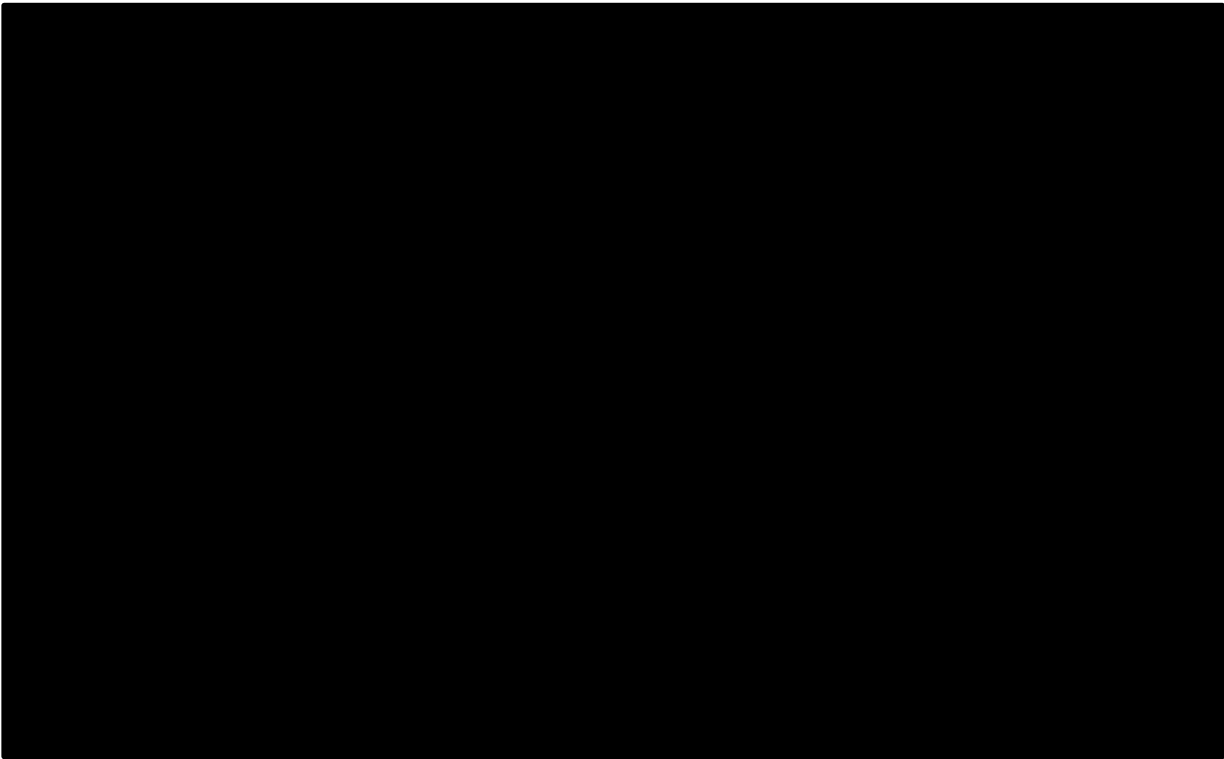
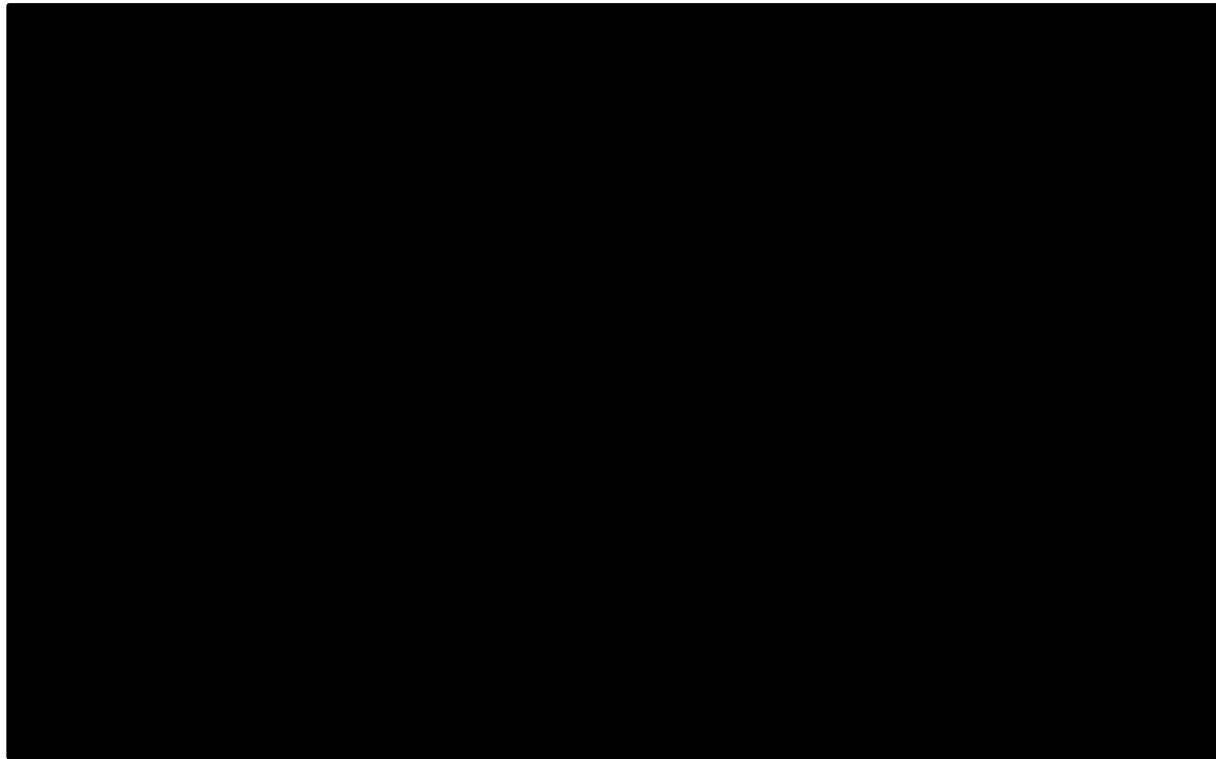


Figure 31: Deterministic sensitivity analysis on incremental QALYs: risdiplam versus nusinersen (type 2/3)



Abbreviations: HR = hazard ratio; HSUV = health state utility value; QALY = quality-adjusted life year

7.3.4.12.2 Company's scenario analysis (types 2 and 3)

Risdiplam across all scenarios when compared independently to nusinersen. When compared to BSC, scenarios that had the largest impact on the ICER were using the health-state related costs from TA588,² using alternative carer utility values from the Roche study, and using alternative health-state utility values from TA588 or utility values from the SUNFISH trial.^{2,53}

Table 72: Company reported scenario analysis results for the type 2/3 SMA model

Scenario	ICER vs BSC	% ICER change	ICER vs nusinersen
Base case		-	
Efficacy scenarios			
Comparative efficacy vs. BSC: set to natural history study			
Risdiplam efficacy informed by non-imputed 5-year SUNFISH (excl. Asia) ⁵³			
Risdiplam efficacy post follow-up set to the extrapolations as seen in the SUNFISH trial period			
Weibull used for type 2 OS extrapolation			
Source for % scoliosis: change to Wijngaarde et al. 2019 ³⁶			
Source for % bulbar dysfunction: change to Wadman et al. 2017 ³⁹			
Source for % respiratory support: change to van der Heul et al. 2019 ⁷³			
HCRU scenarios			
Alignment with TA588 source for HCRU ²			
Utility values scenarios			
Source for patient utility values: TA588 ERG clinical advisors ²			
Source for patient utility values: EQ-5D-3L values from SUNFISH ⁵³			
Source for caregiver utility values: Roche utility survey			
Source for caregiver utility values: UK Burden of Illness Study			
Other scenarios			
Inclusion of VAT saving from risdiplam homecare			
Changing baseline characteristics to REACH UK patient population			
Number of carers lowered to 2			
Number of carers increased to 3			
Discount rate for both costs and benefits is lowered to 1.5%			
Discount rate for benefits is lowered to 1.5%, discount rate for costs remains 3.5%			

Scenario	ICER vs BSC	% ICER change	ICER vs nusinersen
Source: company submission ⁴⁴ Abbreviations: BSC = best supportive care; HCRU = health care resource use; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; OS = overall survival; TA = technology appraisal; UK = United Kingdom			

7.3.5 Model validation and face validity check

The company reported that all models were subject to external quality assurance procedure which involved technical validation of key model inputs and calculations. In addition, face validity of the models was examined by seeking patient and clinical experts' opinion on appropriateness and relevance of the model structure and inputs to ensure the model approach appropriately captured the costs and outcomes in UK clinical practice. An ad-board was run with academic health economics experts to discuss the appropriateness and potential adaptations of the original model from TA755.³

EAG comment: Although the EAG considered the model structure to be appropriate for the decision problem, the EAG has highlighted concerns around the approach used to model uncertainty around relative effectiveness parameters in the Roche model. Moreover, the EAG found multiple small errors across the model files, including an error in the calculation of “not sitting” utilities in the type 2/3 model or assumed differences in disease-related events between risdiplam and OA in the type 1 model. To ensure transparency, the EAG recreated the Markov trace in the Roche models and changed the approach of uncertainty in relative effectiveness using the same model files provided by Roche.

8 Summary and comparison of company submissions

8.1 SLR comparison

The search strategy for the SLR by Biogen (nusinersen) was assessed using the PRESS checklist and met the criteria for reporting. In contrast, the SLR by Roche (risdiplam) did not provide the search strategy and the EAG were unable to assess whether the search strategy lead to a complete overview of the literature.

The Biogen SLR originally considered type 0 and 4 patients, however due to clinical advice and lack data, respectively, they were not assessed further. These subgroups of SMA were not considered in the Roche SLR. The Roche SLR did identify further treatments outside the scope (i.e. reldesemtiv, apitegromab, RO7204239 and Branaplam) as interventions. This means there would be no missing data from this aspect. An issue with the Biogen inclusion criteria was the restriction of sample size (minimum 100 participants). This led to the exclusion of smaller studies, but not controlled studies. The Roche SLR did not make such exclusions. Some concerns are present regarding data extraction for the Roche SLR as there was a lack of detail surrounding the methods used. Additionally, some concerns are raised regarding the Roche SLR quality appraisal methods, due to lack of details.

Overall, there were some concerns regarding the reporting standards of the Roche SLR, while the Biogen SLRs main concern was regarding eligibility criteria.

8.2 ITC comparison

Biogen and Roche both attempted to perform MAIC analyses. Biogen only compared nusinersen with OA in presymptomatic patients using an unanchored MAIC, not with risdiplam. While Roche did compare risdiplam against both nusinersen and OA, these analyses were naïve and utilised only t-tests.

For type 1, Roche and Biogen both compared risdiplam and nusinersen using unanchored MAICs. However, Roche utilised an STC when comparing to OA, whilst Biogen continued using an unanchored MAIC for nusinersen. For type 1 SMA patients, Biogen controlled for the following factors, which Roche did not; sex; age at screening; age at symptom onset; weight; SMN2 copy number; baseline ventilation support (yes/no); and baseline feeding issues (yes/no). Roche stated that sex was not included as a previous prognostic review suggested this variable was not a statistically significant factor. Weight was not included due to lack of data availability. Mean age at symptom onset was not included due to correlations with age at first dose, which was selected in the base case. Ventilatory and/or nutritional support were deemed not viable to use for matching due to differences in practice. The reasons for excluding age at screening and SMN2 copy number as covariates were not provided. Covariates for the modelling were specifically reduced in the Biogen models, if necessary, using a LASSO regression. Roche did not report this.

For type 2/3 patients, Biogen utilised an STC only, as they suggested that the cohorts were not easily comparable. Roche implemented an anchored MAIC and reported the limitations of this, mainly due to lack of comparability between the two cohorts and reduced ESS leading to increased uncertainty. Type 2/3 SMA analyses for both companies utilised the same covariates for matching. The EAG believes that indirect comparisons for the type 2/3 patients is difficult to conduct due to differences in patient eligibility and baseline characteristics. While IPD could potentially balance some of this confounding it is unclear if this would be adequate to overcome these inherent differences in eligibility and patient characteristics. This opinion of

the EAG is also supported by a recent draft report of the same treatments conducted by the Institute for Clinical and Economic Reviews.⁷⁵

8.3 MAA comparison

For the paediatric MAAs nusinersen conducted more MMRMs compared to risdiplam (n = 5 vs 2, respectively), this was likely due to data availability. The main difference was the lack of type 1 MMRM analyses (e.g. CHOP-INTEND, RHS). There were also differences in model covariates, nusinersen included baseline score and duration of disease at baseline, which the risdiplam MMRMs did not. Additionally, for type 2/3 patients nusinersen analyses included baseline function of non-sitters, sitters and walkers. While risdiplam analyses categorised patients as walkers/sitters or non-sitters in type 2/3 models. Overall, both MAAs conducted analyses when feasible and, if not feasible, descriptive statistics were reported.

For the adult MAAs nusinersen and risdiplam conducted the same MMRMs. Efforts were also made to consider the type 2/3 patients as separately as possible. Overall, the analyses are conducted using appropriate methods.

8.4 Cost-effectiveness analysis

Biogen and Roche both conducted cost-effectiveness analyses of treatments for presymptomatic, type 1, and type 2/3 SMA populations separately.

Biogen only compared nusinersen with BSC across all the three population groups citing the reason that it was not appropriate to assess the relative effectiveness of nusinersen against DMTs given the lack of robust evidence on relative effectiveness. The economic model structure in the Biogen submission was based on TA588 and focused on a set of motor-milestones gains and losses defined by the WHO-MM instrument.² For both the presymptomatic and type 1 populations, the model included a transition to permanent ventilation. For the presymptomatic population, Biogen used data from the single-arm NURTURE study and conducted a naïve comparison against BSC using control arm motor milestones data from ENDEAR and CHERISH trials.^{27,28,34} Due to a lack of events, survival assumptions were informed by the approach in HST24.¹⁶ For the type 1 population, Biogen used data from the ENDEAR-SHINE controlled trial and its extension, which informed transitions in motor-milestones, risk of death and risk of permanent ventilation for both nusinersen and BSC.^{27,35} For the type 2/3 population, data were drawn from the CHERISH-SHINE controlled trial and extension study to inform motor milestone transitions for both nusinersen and BSC.^{28,35} Due to a lack of events, survival assumptions in this model were informed by the approach in HST24, as well as general UK population survival.^{16,42}

Trial results from NURTURE indicated that nusinersen
 [REDACTED]
 [REDACTED] In the ENDEAR-SHINE
 study [REDACTED]
 [REDACTED]. Results
 from CHERISH-SHINE suggested that nusinersen
 [REDACTED]
 [REDACTED]
 [REDACTED]

Patient health-related quality of life (HRQoL) data was not collected from either the NURTURE or ENDEAR trials.^{27,34} Instead, the model adopted the HRQoL approach used in HST24 and

applied it across the presymptomatic, type 1, and type 2/3 population models.¹⁶ In the base-case analysis patient and informal carer HRQoL were pooled together using an approach consistent with that applied in TA755.³ As the base-case approach combined HRQoL for both patients and carer, a severity modifier was not applied to the results. Biogen also used cost estimates from HST24 to inform NHS and personal social services costs.¹⁶ The approach to modelling the disease included a long-term risk of motor-milestone decline, based on available clinical trial evidence.³⁹ Additionally, patients receiving nusinersen were also at risk of treatment discontinuation and moving to BSC, as observed in the trial data.³¹

Biogen's base-case analysis indicated that [REDACTED] for treating the presymptomatic population. A subgroup analysis further suggested that [REDACTED]. However, [REDACTED] compared to BSC in the treatment of type 1 and type 2/3 SMA populations. Similar findings were reported in the company's subgroup analyses for the type 2 and type 3 populations.

Roche compared risdiplam with nusinersen and OA for the presymptomatic population. BSC was not deemed an appropriate comparator for the presymptomatic population, as this approach is rarely used in clinical practice for presymptomatic patients. For the type 1 population, risdiplam was compared with nusinersen, OA, and BSC, while for the type 2/3 risdiplam was compared with nusinersen and with BSC. The economic model structure in the Roche submission was based on TA755 and focused on a set of motor milestones gains and losses defined by the HINE-2 instrument for presymptomatic and type 1 patients,³ while the type 2/3 model focused on motor milestones from the MFM-32 and HFMSE instruments.⁴⁴ The presymptomatic and type 1 models also included the risk of permanent ventilation.

For the presymptomatic population, Roche used data from the RAINBOWFISH⁵⁷ single-arm study and assumed equivalence in effectiveness across risdiplam, nusinersen and OA. Data for BSC from an internal, unpublished natural history study was included in the model, but the Roche submission did not consider the BSC results to be a relevant comparator in the decision problem.⁴⁴ For the type 1 population, Roche used data from FIREFISH,⁵⁶ a single-arm trial for risdiplam, and applied the estimates from the unanchored MAIC with ENDEAR to estimate the relative effectiveness of nusinersen and BSC, as well as STRIVE-EU for OA.^{44,65} These data informed model transitions for motor milestones, overall survival, and the risk of death or permanent ventilation (from EFS data). For the type 2/3 population, Roche used data from the SUNFISH study,⁵³ a controlled trial informing transitions between motor milestones for nusinersen and BSC. Due to a lack of events, survival assumptions were informed by pooled survival data from published studies identified in the literature review for type 2 patients, and general population survival for type 3 patients, and an assumption of lower overall survival for BSC.⁴²

Trial results from RAINBOWFISH⁵⁷ suggested risdiplam [REDACTED]. Results from FIREFISH suggested risdiplam [REDACTED]. Results from SUNFISH suggested risdiplam [REDACTED].

[REDACTED]. These key results had the largest implications for disease-related health care costs, patient quality of life and carer quality of life. Patient health-related quality of life (HRQoL) data was not collected from either RAINBOWFISH⁵⁷ or FIREFISH.⁵⁶ Instead, the model adopted the approach to patient HRQoL from TA755,³ applying it through the presymptomatic and type 1 population models. HRQoL for type 2/3 patients was informed by estimates from Lloyd et al. 2019 and trial data on the EQ-5D from SUNFISH was explored as a scenario analysis.^{53,67} The base-case analysis pooled together patient and informal care HRQoL based on an approach used in TA755.³ As the base-case approach combined patient and carer HRQoL, a severity modifier should not be applied to the results.

The submission by Roche used an expert elicitation exercise conducted by the company across type 1, type 2, and type 3 patients to inform NHS-related costs and personal social services costs.⁴⁴ Costs for presymptomatic patients were assumed to be equivalent to type 1 patients. The approach to modelling the disease assumed no long-term risk of motor-milestone decline for patients treated with DMTs. Based on evidence from the trials, the models assumed no risk for treatment discontinuation for risdiplam and extended this assumption to nusinersen; this approach is not clinically plausible for OA and BSC.

Roche's base-case analysis showed that risdiplam would [REDACTED] when treating the presymptomatic population. Even though the comparison with BSC was not deemed appropriate, the company model showed that [REDACTED] when compared to BSC for the presymptomatic population. The company did not conduct a subgroup analysis in the population with 2 or 3 copies of SMN2 due to a lack of comparative evidence. The company's base-case analysis showed that [REDACTED] when compared to nusinersen or OA. However, [REDACTED] treatment when compared to BSC. Risdiplam was [REDACTED] in the treatment of type 2/3 population when compared to nusinersen [REDACTED]

The economic model structures used by the companies were appropriate conceptualisations of the decision problem and disease progression. However, important differences in patient characteristics and the clinical definitions of motor milestones made it difficult to compare the effectiveness of therapies across models. This limitation also affected the interpretation of results from the MAA data, further reducing their applicability to the cost-effectiveness models. Table 73 highlights differences in motor milestone definitions for the presymptomatic and type 1 populations and Table 74 for the type 2 and 3 populations.

Table 73: Motor milestone definitions for presymptomatic and type 1 patient models

Economic model: Biogen submission			Economic model: Roche submission	
Model states	WHO motor milestones	HINE-2 definitions	Model states	HINE-2 definitions
Not sitting	-	< 3 in the HINE-2 sitting dimension	Not sitting	< 1 in the HINE-2 sitting dimension
Sitting without support	Sitting without support	≥ 3 in the HINE-2 sitting dimension to < 2 in the standing dimension	Sitting (with or without support)	≥ 1 in the HINE-2 sitting dimension to < 2 in the standing dimension

Economic model: Biogen submission			Economic model: Roche submission	
Model states	WHO motor milestones	HINE-2 definitions	Model states	HINE-2 definitions
Standing with support	Standing with assistance	≥ 2 in the HINE-2 standing dimension to < 3 in the walking dimension	Standing (with or without support)	≥ 2 in the HINE-2 standing dimension to < 2 in the walking dimension
Walking independently	Walking alone	≥ 3 in the HINE-2 walking dimension	Walking (with or without support)	≥ 2 in the HINE-2 walking dimension
Abbreviations: HINE-2 = Hammersmith Infant Neurological Examination-2; WHO = World Health Organization				

Table 74: Motor milestone definitions for type 2/3 patient models

Economic model: Biogen submission		Economic model: Roche submission	
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'
Abbreviations: HFMSE = Hammersmith Functional Motor Scale - Expanded; MFM-32 = Motor Function Scale – 32 Item; WHO = World Health Organization			

Beyond the limitations arising from differences in clinical outcome measures, the quality of relative effectiveness data available from ITCs further restricted the EAG's ability to assess the relative effectiveness of DMTs in the base-case. As a result, these comparisons had to be explored through scenario analyses. Patient HRQoL was a major source of uncertainty in both submissions, largely due to the challenges of measuring HRQoL in children and the rarity and severity of SMA. The greatest uncertainty stemmed from HRQoL estimates associated with severe health states, such as permanent ventilation, non-sitting and sitting-related states. Indeed, another major source of uncertainty in the cost-effectiveness analysis across both company submissions was the estimation of disease-related costs for the most severe health states, including permanent ventilation, non-sitting and sitting-related states. At these levels of severity, the cost of care can be close to the maximum willingness-to-pay threshold of the

healthcare system. As a result, any treatment that increases costs, regardless of its effectiveness, risks exceeding this willingness to pay threshold. The EAG identified substantial variation in cost estimates for the model health states, driven by a lack of robust data.

Furthermore, the EAG acknowledges that the perspective of informal carers is an important consideration in this disease area, and that NICE guidelines permit the inclusion of carer health-related quality of life (HRQoL) in appraisals. Indeed, discussions between the EAG and patient organisations as part of the MTA process emphasised the impact of SMA on carer HRQoL. However, the company submissions adopted markedly different approaches to incorporating informal carer HRQoL, relying on data elicited outside the clinical trials. Due to these limitations in both data quality and methodology, the EAG adopted the patient perspective to better reflect the severity of the disease, while also presenting a scenario analysis that included both patients and carers.

Overall, clinical results indicated that, in presymptomatic patients, both risdiplam and nusinersen had the potential to improve motor milestones to the least severe levels of the disease and reduce the risk of permanent ventilation. However, the evidence was insufficient to draw strong conclusions compared to BSC. For type 1 patients, both treatments appeared to reduce the risk of permanent ventilation and maintain motor function around sitting-related health states, although significant evidence gaps remained for risdiplam. In patients with type 2 and 3 SMA, there was stronger evidence that both treatments helped maintain motor milestones related to sitting when compared to BSC. These findings have important implications for the economic analysis, as the costs of care in sitting-related health states are substantial and must be weighed against gains in patient quality of life. However, this also constrains the analysis to motor milestones measured by instruments that may lack sensitivity to fully capture the disease's complexity.

Although the economic analyses submitted by both companies combined patient and carer quality of life meaning that results were not eligible for the severity modifier criteria, Table 75 presents the eligibility for nusinersen and risdiplam across each patient population to the severity modifier criteria based on QALYs in standard care.

Table 75 Severity modifier eligibility based on the economic evidence presented by each company

Population	Expected QALYs	BSC QALYs	Absolute shortfall	Proportional Shortfall	Eligible severity modifier
Biogen - nusinersen					
Presymptomatic	24.89				1.2
Type 1	24.87				1.7
Type 2&3	24.55				1.2
Roche - risdiplam					
Presymptomatic	24.87				1.7
Type 1	24.87				1.7
Type 2&3	24.02				1.7
Abbreviations: QALY = quality adjusted life year; BSC = best supportive care					

9 Involvement and engagement with companies, professionals and patients

Throughout the MTA process, the EAG consulted with both Biogen and Roche, representatives of professional organisations, representatives of patient organisations and individual clinicians. Three meetings each were held separately with each of Biogen and Roche, representatives of professional organisations, and representatives of patient organisations. The discussions in these meetings informed the overall approach to the MTA and the methods the EAG proposed to use, as well as providing feedback on high-level, interim results. The EAG met with other clinicians on an individual, ad-hoc basis to help validate clinical assumptions made.

An overall summary of the meeting dates with each stakeholder and a brief overview of the agenda for each meeting is provided in Table 76.

Table 76: Overview of meetings between the EAG and key stakeholders

Date	Who the EAG met with	Key discussion points
18.03.2025	Biogen	• Exploration of additional PfC
26.03.2025	Roche	• Exploration of additional PfC
31.03.2025	Clinicians and professional organisations	• High level overview of the overall approach and methods being taken by the EAG • Key considerations to inform the review question • Early economic modelling designs and considerations • Qualitative data reflections • Discussion and agreeing next steps
04.04.2025	Patient organisations	• High level overview of the overall approach and methods being taken by the EAG • Key considerations to inform the review question • Early economic modelling designs and considerations • Qualitative data reflections • Discussion and agreeing next steps
10.04.2025	Clinician	• Prognostic factors • Reasons for delay in diagnosis • Choices of treatment • Discussion of different outcomes and their lack in picking up important factors • Reasons for discontinuation • Rate of loss of function
28.04.2025	Specialist physiotherapist	• Experience of treating patients with different types of SMA and their characteristics, impact on quality of life
06.05.2025	Roche	• Overview of the EAG assessment of the Roche submission and changes made by the EAG to the Roche decision problem, the clinical evidence, and the economic model. • Discussion of the EAG changes to the Roche submission.

Date	Who the EAG met with	Key discussion points
06.05.2025	Patient organisations	• Reflection on major points from previous meeting and what the EAG have considered surrounding these • Presenting an overview of the structure of the economic models, including the anticipated outcomes, costs and utilities feeding into each model • Overview of the EAG's approach to the qualitative analyses and interim results • Discussion and space for questions and answers on each of the key points covered
07.05.2025	Biogen	• Overview of the EAG assessment of the Biogen submission and changes made by the EAG to the Biogen decision problem, the clinical effects, and the economic model. • Discussion of the EAG changes to the Roche submission.
07.05.2025	Professional organisations	• Reflection on major points from previous meeting and what the EAG have considered surrounding these • Presenting an overview of the structure of the economic models, including the anticipated outcomes, costs and utilities feeding into each model • Overview of the EAG's approach to the qualitative analyses and interim results • Discussion and space for questions and answers on each of the key points covered
09.05.2025	Specialist physiotherapist	• Differences between type, with consideration of natural history, in adult patients • Timing of assessments for patients • Changes in motor milestones and the large spectrum of potential motor changes • Impact of fatigue and how treatment may improve this
20.05.2025	Registry	• Availability of data and updating of modelling where possible • Timeframes for getting any further updates, if available
10.06.2025	Clinician	• Follow-up meeting to discuss permanent ventilation and drug side effects
16.06.2025	Biogen	• Recap of the EAG base-base models and scenarios surrounding nusinersen • Presentation of interim ICER results and discussion
17.06.2025	Clinicians and professional organisations	• Reflection on major points from previous meeting and what the EAG have considered surrounding these

Date	Who the EAG met with	Key discussion points
		• Update on methods used for the qualitative analysis following previous meeting • Summary of the approach to the SLR and comparison of information used to inform SLRs for nusinersen and risdiplam • Recap of the EAG base-case economic models and scenarios for both nusinersen and risdiplam • High-level presentation of overall results for the economic models • Discussion and space for questions and answers on each of the key points covered
18.06.2025	Roche	• Recap of the EAG base-base models and scenarios surrounding risdiplam • Presentation of interim ICER results and discussion
18.06.2025	Patient organisations	• Reflection on major points from previous meeting and what the EAG have considered surrounding these • Update on methods used for the qualitative analysis following previous meeting • Summary of the approach to the SLR and comparison of information used to inform SLRs for nusinersen and risdiplam • Recap of the EAG base-case economic models and scenarios for both nusinersen and risdiplam • High-level presentation of overall results for the economic models • Discussion and space for questions and answers on each of the key points covered
Abbreviations: EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; SLR = systematic literature review; SMA = spinal muscular atrophy		

10 EAG qualitative analysis methods

10.1 Data sources

To identify areas of key concern surrounding living with SMA, as well as surrounding the benefits of nusinersen and risdiplam from the perspective of those with a lived experience of SMA, the EAG conducted qualitative analyses. Insofar as possible, the process was guided by the principles of the CLIP-Q approach to rapid qualitative research, particularly the principles surrounding data collection and analysis.⁷⁶

The EAG used the following sources to inform the analyses.

- Transcripts of meetings the EAG have had with professional and patient organisations, arranged by NICE
- Patient organisation submissions to NICE⁷⁷⁻⁷⁹
- Professional organisation submissions to NICE⁸⁰
- Professional expert submissions to NICE⁸¹
- Patient expert submissions to NICE⁸²⁻⁸⁴
- Case studies included as part of the appendix provided by SMA UK, Muscular Dystrophy UK and SMA Reach⁸⁵
- Select quotations included as part of the appendix provided by SMA UK, Muscular Dystrophy UK and SMA Reach⁸⁵
- Free-text data for adult and paediatric populations provided to the EAG by SMA REACH UK⁸⁶⁻⁸⁹

10.2 Coding framework

As much as possible, the EAG adopted the principles of the CLIP-Q approach for rapid qualitative research, taking a pragmatic approach to data analysis that utilised both deductive and inductive approaches.⁷⁶ As such, a framework analysis was undertaken, focusing on identifying the issues of most importance to people with a lived experience of SMA, as well as the impacts of treatment with nusinersen and risdiplam.

Following discussions with patient and professional groups, the EAG sought to develop an initial coding framework. Two members of the EAG (EEJ and NOC) iteratively developed the final framework over two phases of piloting. The framework included all outcomes from the NICE decision problem for the MTA,⁶ as well as themes that were raised as important issues in initial meetings the EAG held with professional and patient groups. Inductive codes could also be added to the framework if new concepts and themes arose during the coding process; these were discussed and agreed upon by the two researchers.

The final coding framework was as follows.

- Ability to socialise
- Activities of daily living
- Adverse events
- Bulbar function
- Complications of SMA (e.g. scoliosis, contractures)
- Economic considerations (e.g. resource use, use of health or social services)
- Equality considerations
- Hospitalisation

- Impact on ability to work
- Impact on education
- Impact on families and carers
- Independence
- Looking to the future (e.g. increased hope for the future, anticipatory grief)
- Maintenance or stability of condition
- Mortality
- Motor function
- Need for non-invasive or invasive ventilation
- Patient choice
- Psychological impact (e.g. impact on mental health or wellbeing)
- Quality of life
- Respiratory function
- Spectrum of SMA (e.g. differences in functional ability within SMA types)
- Stamina and fatigue

Because independence and quality of life could be impacted by many aspects of living with SMA and treatments for SMA, these were considered to be themes that cut across many of the other domains. As such, the pragmatic decision was taken to only utilise these codes when independence, dependency or quality of life were explicitly mentioned within any of the sources.

10.3 Data coding

The coding framework was transferred to the software Nvivo for coding. File classifications were created within Nvivo to identify the following characteristics for each piece of data coded.

- Source: as listed above
- Respondent: PPI group; professional group; patient expert; professional group; patient – adult; patient – child; carer; not known
- SMA type: Type 0; Type 1; Type 2; Type 3; Type 4; not known
- Treatment: nusinersen; risdiplam; Zolgensma (OA); nusinersen, risdiplam and OA; nusinersen and OA; not known

In accordance with CLIP-Q guidance, a team-based, collaborative approach to coding was undertaken.⁷⁶ First, two members of the EAG (EEJ and NOC) undertook two pilot coding phases, independently coding three data sources each within Nvivo. The results of the pilot coding phase were discussed to help establish concordance between the coders and identify areas where the coding framework could be modified.

Subsequently, both members of the EAG independently coded a third of the sources independently, comparing coding upon completion of this batch to further ensure a level of agreement. The level of agreement between reviewers for each file and code was compared by generating coding reports within Nvivo. If agreement was below 80%, the two researchers would examine and discuss the difference, noting these in a coding log. The remaining sources were then coded by a single EAG researcher (EEJ) and checked by other (NOC). Any potentially missing or erroneous codes identified by the second researcher were discussed and agreed prior to analysis.

10.4 Analysis and reporting

Following coding, both EEJ and NOC worked to interrogate the data coding, identifying key subthemes from the framework inductively; these related to the impact of SMA on patients' and carers' lives, as well as the impact of treatment. A collaborative approach between researchers was taken to identify the main connections and subthemes from the coded data.

An initial, visual analysis of the coded data were taken to two further meetings with professional and PPI groups in May 2025; this interim analysis did not contain any qualitative data from registries as these data had not been received at that point. The findings were discussed to validate the findings at an interim stage, make any adjustments to wording or analysis approach, and to more broadly discuss what had been found through the qualitative analysis to that point.

Following this step, both researchers wrote narratives surrounding the major themes and subthemes identified from the coding phase, including illustrative quotations where appropriate. The narratives were written from a pragmatic perspective to present the findings of the qualitative data without additional theory generation or interpretation. This step was repeated when free-text data from the registry was received to fully update the qualitative analysis and ensure comprehensiveness. Where quotations were included, contextualisation was added by noting who provided the quotation (e.g. a person with SMA or their carer, patient or professional group submission, or discussion with the EAG) and the type of SMA the individual or the individual they were caring for had (if known). For quotations derived from registry data, the age of the patient and the length of time they had been on treatment when the comment was submitted were presented. For the paediatric registry data, we also included information about their functional status (e.g. sitter, walker) and their SMA type, where possible. This information was not available for the adult registry data.

Once written, researchers read, commented on and discussed the written narratives together, in order to ensure that there were no potentially missing sub-themes, that the narratives were written from the aforementioned pragmatic standpoint, and that the narratives and direct quotations used were adequately contextualised (e.g. by source and demographic information) wherever possible.

10.5 Role of reflexivity

The qualitative component of the EAG report was undertaken by two researchers. Both researchers had some experience of qualitative coding and analysis from prior research projects. One of the reviewers had no prior experience of research within the SMA community, while the other had previously worked on research relating to the condition. Neither of the researchers involved in the qualitative coding had a clinical background. Both researchers regularly met to debrief regarding the data coding and analysis processes, allowing room to reflect on their perspectives and interpretations when drawing any conclusions from the data.

10.6 Limitations of the qualitative analyses

The qualitative analysis had several limitations. Firstly, the use of a framework analysis, while appropriate for the timescale of the project and linking the qualitative analysis to the decision problem for the MTA, meant that a deeper exploration of the data through thematic analysis was not undertaken.

The information taken from the case studies and quotations provided by SMA UK, Muscular Dystrophy UK and SMA Reach were not originally intended for the purpose of this MTA.⁸⁵

There were also often very few details reported about the respondents' demographics or the treatment that they were undergoing. This meant that it was often challenging to be able to directly connect any changes in the respondents' health and wellbeing with either nusinersen or risdiplam. A similar issue was present for the registry data. In discussion with the EAG, members of the registries noted that some of the symptoms and experiences of those providing free-text were not always attributable to nusinersen or risdiplam. As such, the EAG did not attribute any treatment effects to either nusinersen or risdiplam where this information was not explicit, instead commenting on these instances as the effects of treatment more generically. However, this meant that it was not always possible to differentiate between the treatments and peoples' experiences of both nusinersen and risdiplam.

Furthermore, the registry data used had other caveats. Firstly, the adult registry data was limited by a lack of demographic information. While we attempted to contextualise any quotations and narratives using the information provided, it was not possible to include details such as their SMA type, functional status and age at diagnosis. In discussions between the registries and the EAG, it was also noted that the people providing free-text data for the paediatric data were not always the primary caregiver for the child. As it was not possible to discern when this was the case, the EAG were not able to provide this context within the analyses and report.

Finally, the EAG had originally planned to weave the results of the qualitative analysis consistently throughout the full report. However, as the EAG decided that the evidence for nusinersen and risdiplam were not directly comparable (see Section 11.6.2 for an explanation), the resulting report structure meant it was not possible to feed the qualitative analysis through the results. As such, the qualitative analysis is presented in two standalone sections within the clinical effectiveness and cost-effectiveness results (see Sections 13.5 and 15.3).

11 EAG clinical effectiveness SLR methods

11.1 Objective and methods

The EAG ran update searches and incorporated newly published data into the original systematic review;¹ the previous work was not repeated, except to screen previously excluded studies for eligibility, and to critically appraise the main company trials.

Systematic review methods were based as far as possible on those in the Cochrane Handbook, with the caveat of time limitations.⁹⁰

11.2 Inclusion and exclusion criteria

The eligibility criteria for the EAG review are reported in Table 77.

Table 77: Inclusion and exclusion criteria for EAG SLR

Domain	Inclusion criteria	Exclusion criteria
Population	People with types 0, 1, 2, 3 or 4 5q SMA, or presymptomatic 5q SMA confirmed with genetic testing with 1 to 4 SMN2 copies.	- Received spinal fusion surgery following a diagnosis of scoliosis (prohibits safe administration of nusinersen) - Hospitalisation or respiratory conditions history or planned at the time of screening or tracheostomy. - History of surgery for scoliosis or hip fixation - Presence of clinically relevant ECG abnormalities before study drug administration - Unstable gastrointestinal, renal, hepatic, endocrine or cardiovascular system diseases - Any in vitro studies
Interventions	- Nusinersen - Risdiplam Interventions are monotherapies in addition to existing clinical services and established clinical management. Onasemnogene abeparvovec	- Concomitant or previous participation in any investigational drug - Any history of cell therapy
Comparators	- Established clinical management - Best supportive care In addition, for children aged 12 months and under with a bi-allelic	None

Domain	Inclusion criteria	Exclusion criteria
	mutation in the SMN1 gene and present with a clinical diagnosis of type 1 5q SMA or presymptotically with up to 3 copies of the SMN2 gene • Onasemnogene abeparvovec • Placebo control • Sham control	
Outcomes	• Motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills) • Bulbar function (including, for example, swallowing and ability to communicate) • Frequency and duration of hospitalisation • Respiratory function • Complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation • Stamina and fatigue • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers) • Ability to socialise^a • Activities of daily living^a • Psychological impact^a • Impact on ability to work^a • Impact on education^a • Impact on family and carers^a • Independence^a • Looking to the future^a • Maintenance or stabilisation of disease^a • Patient choice^a • Spectrum of SMA^a	No exclusion criteria
Subgroups	• Number of SMN2 gene copies in people with presymptomatic SMA	

Domain	Inclusion criteria	Exclusion criteria
	- Functional status (non-sitter, sitter, walker) - People who have had prior active treatment for SMA	
Study design	Controlled studies: RCT, non-randomised studies, case/control, cohort studies Non-controlled studies: before-after studies, longitudinal observational studies	- Case series - Case reports - SLRs^b - Studies containing fewer than 20 participants
Publication types	- Journal articles - Conference abstracts	- Editorials - Commentaries
^a Outcomes added after consultation with patients, for the update only ^b SLRs and meta-analyses were included past the abstract screening stage to enable reference checking but were excluded at full-text stage. Abbreviations: ECG = electrocardiogram; HRQoL = health-related quality of life; RCT = randomised controlled trial; SLR = systematic literature review		

Qualitative studies were not formally included. However, stakeholder insights were incorporated into the review from stakeholder submissions and the free text fields of quality of life tools (see Section 9 above).

The following differences exist between the previous review eligibility criteria and the update review eligibility criteria:

- The interventions were not compared directly to each other^{11.6.2}.
- Conference abstracts were included in the update if they reported results from eligible studies and provided sufficient data for extraction (these were not included in the previous SLR).
- Following consultation with key stakeholders (e.g. patient advisors, carers, professionals) to ensure that the most relevant outcomes and outcome measures were captured, and a list of extra outcomes not specified in the decision problem but considered to be important were added (Table).

11.3 Identification of studies

Literature searches implemented for the previous SLR were critiqued to ensure they were comprehensive before re-running the searches to include studies published up to March 2025.

Searches for effectiveness evidence were implemented in: biomedical databases (Medline and Embase); an interdisciplinary database (Web of Science); clinical trial registries (Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov); and the Cochrane Library, which indexes systematic reviews of medical interventions. Search terms pertained to the population, interventions and outcomes of interest.

Based on the previous searches, databases were searched from 2017 for publications reporting data on nusinersen and from 2020 for publications reporting data on risdiplam, which corresponds to the dates when the technology appraisal (TA) submissions were made by the

companies for each drug. The pivotal clinical trials for these drugs were registered pre- 2017/ 2020, therefore search restrictions were not applied in ClinicalTrials.gov. Searches were limited to studies published in English language.

The search critique and Medline search strategy are available in Appendix 1 (Section 19).

The reference lists of relevant systematic literature reviews and meta-analyses captured in the searches were screened to identify primary studies that were eligible for inclusion in this systematic review update.

The excluded studies list from the previous review was scrutinised for studies meeting the edited eligibility criteria.

11.4 Data collection

11.4.1 Screening

Multiple reviewers independently assessed the relevance of a sample of retrieved records based in stage 1 on title and abstract, and in stage 2 on full text in relation to the eligibility criteria. Any conflicts at each stage were resolved via a discussion between the screening team; the remaining records were then screened by one reviewer, who discussed with a second reviewer in case of uncertainty.

11.4.2 Data extraction

A data extraction form was created in Excel and piloted on a sample of included studies and included items from the previous systematic review: study characteristics; participant characteristics; intervention details; outcomes; and results. One person extracted data from each study, while a second reviewer checked the extracted data for accuracy.

11.5 Critical appraisal

The methodological quality of RCTs and non-randomised studies was assessed using the Risk of Bias 2 (RoB2) and the Risk of Bias in Non-randomised Studies – of Interventions (ROBINS-I) V2 tools, respectively.^{91,92} Critical appraisal was undertaken by one reviewer and checked for accuracy by a second reviewer. Any disagreements between the reviewers were resolved by discussion with adjudication by a third reviewer. Risk of bias assessments were not undertaken for uncontrolled studies; timelines did not allow for formal assessment of risk of bias for the volume of uncontrolled studies found, and they were assumed to be at high risk of bias.

11.6 Data synthesis

11.6.1 Narrative synthesis

Data were grouped within a narrative synthesis according to the type of intervention, comparator and outcomes assessed. Within those groupings, a best available evidence approach was used, with data from the highest quality studies reported first.

11.6.2 Indirect treatment comparison

The EAG considered that conducting an ITC to evaluate the effectiveness of nusinersen versus risdiplam was inappropriate. The trials that would have provided the most robust patient data for comparative evaluation are CHERISH and SUNFISH, both of which recruited type 2/3 patients who could sit independently and included a 'control' arm to provide the indirect data.

However, patients were excluded from the CHERISH trial if they had severe contracture or scoliosis (Cobb angle > 40). Patients with these characteristics were not excluded from the SUNFISH trial: 28% and 38% of the risdiplam and placebo group respectively would not have been eligible for CHERISH due to their scoliosis. Participants in the SUNFISH trial recorded lower HFMSE scores than those in CHERISH and were older on average. An ITC assumes that patients would be equally as eligible and as likely to be allocated to any of the candidate arms, but in reality the administration routes and settings are so different for risdiplam and nusinersen that the EAG considered that this was not the case. It is also unclear that an oral liquid placebo is comparable to a sham injection.

12 EAG economic assessment methods

12.1 Systematic review of existing cost-effectiveness evidence

A previously conducted systematic review of studies evaluating the cost-effectiveness of disease modifying therapies (DMTs) (e.g. risdiplam, nusinersen, onasemnogene abeparvovec) used in the treatment of SMA was updated following standard guidelines.⁹⁰ The following sections describe methods undertaken in the previous systematic review conducted in January 2024, and in this update (January 2024 to present). The results from the original systematic review are summarised in Section 1414, along with the results from this review update.

12.1.1 Objectives

In the original systematic review, the first objective was to summarise the evidence identified on modelling techniques, structures and inputs (including clinical, survival analysis methods, resource use and costs, utility estimates) that were required to generate the models, assumptions and key outcomes. The second objective was to identify key issues that should be considered in model-based economic analyses conducted in the future.

In this review update, the same objectives were applied to evidence identified after January 2024, evaluating the cost-effectiveness of DMTs used in the treatment of SMA.

12.1.2 Inclusion and exclusion criteria

The eligibility criteria applied in the original systematic review are described in the following sections below and were applied in this update without any amendments. The eligibility criteria are presented in Table 78.

Table 78: Eligibility criteria for the SLR of economic evaluations

Eligibility domain	Criteria
Population	• People with types 0, 1, 2, 3 or 4 5q SMA, or presymptomatic 5q SMA confirmed with genetic testing with 1 to 4 SMN2 copies.
Intervention(s)	• Nusinersen monotherapy • Risdiplam therapy
Comparator(s)	• Established clinical management • Best supportive care • The interventions will be compared to each other Additionally, for children aged 12 months and under with a bi-allelic mutation in the SMN1 gene and present with a clinical diagnosis of type 1 5q SMA or presymptotically with up to 3 copies of the SMN2 gene: • onasemnogene abeparvovec
Outcome(s)	• LYG • QALYs
Study design(s)	• All types of economic evaluations (cost-effectiveness, cost-utility, cost-benefit, cost-consequence, or cost minimisation analyses). • Only full publications in the English language were considered, although relevant non-English studies were mentioned.

Eligibility domain	Criteria
Abbreviations: LYG = life years gained; QALY = quality adjusted life year; SLR = systematic literature review; SMA = spinal muscular atrophy; SMN2 = survival motor neuron 2	

12.1.3 Identification of studies

In the previous review, searches were conducted in January 2024 and were reported to comprise searching electronic bibliographic databases and other online sources and contacting experts in the field, followed by examining included studies and a selection of recent, relevant systematic reviews. An information specialist alongside the review team, was reported to have developed the search strategy including terms for SMA, onasemnogene abeparvovec, nusinersen, and risdiplam, with a validated economic evaluation filter where relevant. The searches used incorporated both free-text and thesaurus terms (MeSH/EMTREE), which were initially developed in Embase (Ovid) and stated to be peer-reviewed by a second specialist before being translated to other databases.

In the original review, the searches were conducted between 30 and 31 January 2024 in the following bibliographic databases: Embase (Ovid); MEDLINE All (Ovid); International HTA database (INAHTA); Science Citation Index and Conference Proceedings (Web of Science); CEA Registry (Tufts Medical Center); and EconPapers (RePec). Additionally, database searches were stated to be supplemented by a targeted Google search (31 January 2024) and by a review of selected international HTA and regulatory agency websites (25 January 2024), including: NICE, the Scottish Medicines Consortium, Canadian Agency for Drugs and Technologies in Health, the Institute for Clinical and Economic Review, U.S. Food and Drug Administration, Medicines and Healthcare Products Regulatory Agency and European Medicines Agency.

For this review update, the EAG re-ran the searches on 11 March 2025 to identify new publications since January 2024. Full details of the Medline search are provided in Appendix 1 (Section 19.1).¹⁹ Searches for the economics review were run in: The International Network of Agencies for Health Technology Assessment (INAHTA); Research Papers in Economics (RePec); and Cost-Effectiveness Analysis (CEA) Registry. No search limits were placed.

12.1.4 Data collection

12.1.4.1 Screening

In the previous systematic review, a pilot screen was performed using the predefined inclusion criteria. Two independent reviewers identified relevant records by first screening the titles and abstracts of all records retrieved from the searches. Potentially relevant records were then screened at full text. Any conflicts between reviewer decisions were reported to be resolved by discussion or by consultation with a third reviewer. The progression of records in during screening and reasons for their exclusion at full text was documented using a PRISMA flow diagram.⁹³

In this review update, after deduplication 2472 records retrieved in the updated searches were uploaded to an Excel spreadsheet. Then, the same process as described above for identifying relevant records in the previous review were followed.

12.1.4.2 Data extraction strategy

In the previous systematic review, an a priori pre-piloted data extraction sheet¹⁹ in tabular form using items recommend by Wijnen et al. was used to extract data from all included records (see Appendix 3, Section 19.3).⁹⁴ Information was extracted on items including: study

details and funding; patient characteristics; types of intervention; methods; and outcomes of economic evaluations. The original review stated that if data was found to be missing or not clearly stated, the corresponding author was contacted. Data was assumed to be unavailable if no response was received. Data extraction was performed by one reviewer and cross-checked by a second reviewer. Any disagreements were reported to be resolved by discussion or consultation with a third reviewer.

In this review update, the same data extraction sheet uploaded to Excel was used to extract relevant information from included records. One reviewer carried out the data extraction, which was checked by a second reviewer.

12.1.5 Reporting and methodological quality assessment

In the previous systematic review, the critical appraisal strategy involved assessing all included economic evaluations using the Consolidated Health Economic Evaluation Reporting Standard (CHEERS) 2022 checklist,⁹⁵ as well as appraising records against the Philips' checklist.⁹⁶ Each record was assessed by one reviewer and checked by a second reviewer, with any disagreements being resolved by discussion or consultation with a third reviewer.

In the current review update, for consistency and transparency, included records were evaluated using the CHEERS and Philips' checklist. The EAG acknowledges that the CHEERS 2022 checklist was developed for guiding the reporting of identifiable, interpretable and useful health economic evaluations, not as critical or quality appraisal tool.⁹⁵

12.1.6 Methods of data synthesis

In the original review, a narrative summary of the included economic evaluations was presented alongside summary tables. An overview of the evidence across studies, including their economic modelling approach, key drivers of cost-effectiveness and sources of uncertainty, was presented with recommendations for future economic modelling. In this update, the findings from the previous systematic review were summarised, with relevant new evidence added to the existing summary table and narrative summary.

12.2 EAG cost-effectiveness analysis

The EAG assessed the economic evaluation models submitted by Biogen and Roche for presymptomatic, type 1 and type 2/3 SMA populations. Considering the differences in population characteristics for nusinersen and risdiplam, and to avoid any bias arising out of these differences, the EAG base-case analysis utilised the models submitted by Biogen to compare nusinersen versus BSC, and the models submitted by Roche to compare risdiplam versus BSC.

Based on the considerations in the preceding sections of this EAG report, the EAG defined an EAG base-case for each of the SMA populations. This EAG base-case models included several adjustments to each of the company base-case and these adjustments are summarised in sections 12.2.1 and 12.2.2 below. These adjustments have been broadly categorised into three categories (derived from Kaltenthaler 2016) below.⁹⁷

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the EAG considers that reasonable alternative assumptions are preferred)

12.2.1 Nusinersen using Biogen models

12.2.1.1 Presymptomatic population

The key changes made by the EAG to the Biogen presymptomatic model are summarised in Table 79.

Table 79: Changes made by the EAG to the Biogen presymptomatic model

Input	Biogen base-case	EAG changes	Section
Decision problem	Nusinersen vs BSC	Same as company submission, however exploratory analysis for nusinersen vs OA undertaken.	6.3.1
Time horizon (years)	100	Same as the company submission.	6.3.2.4
Model state transitions	Nusinersen: Based on NURTURE ³⁴ trial BSC: Based on ENDEAR ²⁷ and CHERISH ²⁸ trials.	Same as the company submission	6.3.2.1
Relative effectiveness	BSC- ENDEAR ²⁷ and CHERISH ²⁸ trials	Same as the company submission for BSC, however for the exploratory nusinersen vs OA, the difference in	6.3.2.5

Input	Biogen base-case	EAG changes	Section
		proportions of state occupancy taken from unanchored MAIC of SPR1NT data ³¹	
Treatment effect duration*	Nusinersen: 72 months (Relative rate of decline after this period from treatment response in ENDEAR ²⁷ and CHERISH ²⁸) BSC: 15 months (Baseline probability of decline from Wadman et al. ³⁹ after this period.)	Same as the company submission, however for the exploratory nusinersen vs OA, the treatment effect duration and the relative rate of decline for OA was considered equal to nusinersen.	6.3.2.5
Survival	Overall survival for health states, “sitting without support”, “not sitting” and “permanent ventilation” taken from HST24 ¹⁶ . The overall survival for health states “standing without support” and “walking independently” was informed by the UK general population mortality data from 2017-19. Both the nusinersen and BSC were assumed to have equal survival data.	Same as the company submission, however the most recent UK general population mortality estimates (2021-23) were used. ⁴² In the exploratory analysis, it was assumed that OA survival data equivalent to nusinersen.	6.3.2.10
Discontinuation	Treatment discontinuation for nusinersen based on MAA ¹⁸ data	Same as company submission, however most recently updated MAA ¹⁸ data was used. In the exploratory analysis, it was considered inappropriate to have	6.3.2.11

Input	Biogen base-case	EAG changes	Section
		discontinuation from OA, as it is a one-off treatment.	
Health related quality of life	Health state utility values from HST24 ¹⁶ , and it was assumed that disease modifying therapy increases utility by 10%	Same as company submission. In the exploratory analysis, OA was also assumed to have a utility increment of 10%.	6.3.2.6
Carer health related quality of life	Carer utility increments from TA755 ³ were considered in the base-case analysis	Carer utility from TA755 ³ was not considered in the base-case analysis; however its impact was assessed in the scenario analyses using utilities from Lo et al, 2022. ⁷¹ as they were more recent UK data.	6.3.2.7
Health care resource utilisation	Health state costs informed by HST24 ¹⁶ and TA755 ³	Same as the company approach; however, the costs were inflated to the most recent price year.	6.3.2.8
*After the treatment effect period, patients are assumed to maintain the motor milestones achieved to that point and are at risk of losing motor milestones but cannot gain higher motor milestones after this period. Abbreviations: BSC = Best supportive care; OA = onasemnogene abeparvovec; MAA = Managed Access Agreement; MAIC = matching-adjusted indirect comparison; NICE = National institute for health and care excellence; TA = technology appraisal; HST = highly specialised technology; UK = United Kingdom			

12.2.1.2 Type 1 population

The key changes made by the EAG to the Biogen type 1 model are summarised in Table 80.

Table 80: Changes made by the EAG to the Biogen type 1 model

Input	Biogen base-case	EAG changes	Section
Decision problem	Nusinersen vs BSC	Same as company submission, however exploratory analysis	6.3.1

Input	Biogen base-case	EAG changes	Section
		for nusinersen vs OA undertaken.	
Time horizon (years)	100 years	Same as the company submission	6.3.3.4
Model state transitions	For both nusinersen and BSC: based on data from ENDEAR ²⁷ and SHINE ³⁵ trials	Same as the company submission	6.3.3.1.2
Relative effectiveness	BSC-ENDEAR ²⁷ trial	Same as the company submission for BSC, however for the exploratory nusinersen vs OA, the difference in proportions of state occupancy taken from unanchored MAIC of STRIVE data ³¹ .	6.3.3.5
Treatment effect duration*	Nusinersen: 60 months (Relative rate of decline after this period from treatment response in ENDEAR ²⁷) BSC: 12 months (Baseline probability of decline from Wadman et al ³⁹ after this period)	Same as the company submission, however for the exploratory nusinersen vs OA, the treatment effect duration and the relative rate of decline for OA was considered equal to nusinersen.	6.3.3.5
Survival	Overall survival for health states, “sitting without support”, “not sitting” and “permanent ventilation” from ENDEAR ²⁷ and SHINE ³⁵ . The data for these states in BSC came from ENDEAR ²⁷ . The overall survival for health states “‘standing without support’ and	Same as the company submission, however the most recent UK general population mortality estimates (2021-23) ⁴² were used. In the exploratory analysis, it was assumed that OA survival data equivalent to nusinersen.	6.3.3.9

Input	Biogen base-case	EAG changes	Section
	'walking independently' was informed by the UK general population mortality data from 2017-19. Joint Weibull model was used for overall survival; and for permanent ventilation log normal model was used in the nusinersen arm, while log-logistic was used in the BSC arm.		
Discontinuation	Treatment discontinuation for nusinersen based on MAA) ¹⁸ data	Same as company submission, however most recently updated MAA)¹⁸ data was used. In the exploratory analysis, it was considered inappropriate to have discontinuation from OA, as it is a one-off treatment.	6.3.3.10
Health related quality of life	Health state utility values from HST24 ¹⁶ , and it was assumed that disease modifying therapy increases utility by 10%	Same as company submission. In the exploratory analysis, OA was also assumed to have a utility increment of 10%.	6.3.3.6
Carer health related quality of life	Carer utility increments from TA755 ³ were considered in the base-case analysis	Carer utility from TA755 ³ was not considered in the base-case analysis; however, its impact was assessed in the scenario analyses using utilities from Lo	6.3.2.7

Input	Biogen base-case	EAG changes	Section
		et al, 2022 ⁷¹ as they were more recent UK data.	
Health care resource utilisation	Health state costs informed by HST24 ¹⁶ and TA755 ³	Same as the company approach; however, the costs were inflated to the most recent price year.	6.3.3.7
*After the treatment effect period, patients are assumed to maintain the motor milestones achieved to that point and are at risk of losing motor milestones but cannot gain higher motor milestones after this period. Abbreviations: BSC = Best supportive care; OA = Onasemnogene Abeparvovec (Zolgensma); MAA = managed access agreement data from REACH registries; NICE = National institute for health and care excellence; TA = NICE technology appraisal; HST = NICE highly specialised technology.			

12.2.1.3 Type 2/3 population

The key changes made by the EAG to the Biogen type 2/3 model is summarised in Table 81.

Table 81: Changes made by the EAG to the Biogen type 2/3 model

Input	Biogen value	EAG changes	Section
Decision problem	Nusinersen vs BSC	Same as company submission	6.3.1
Time horizon (years)	100 years	Same as the company submission	6.3.4.4
Model state transitions	For both nusinersen and BSC: based on data from CHERISH ²⁸ and SHINE ³⁵ trials	Same as the company submission	6.3.4.1.2
Relative effectiveness	BSC-CHERISH and SHINE ³⁵ trials	Same as the company submission.	6.3.4.5
Treatment effect duration*	Nusinersen: 96 months (Relative rate of decline after this period from treatment response in CHERISH ²⁸) BSC: 15 months	Same as the company submission.	6.3.4.5

Input	Biogen value	EAG changes	Section
	(Baseline probability of decline from Wadman et al ³⁹ after this period)		
Survival	Overall survival for health states, “sitting without support”, “not sitting” from HST24 ¹⁶ ,. The overall survival for health states “standing without support’ and ‘walking independently’ was informed by the UK general population mortality data from 2017-19. Both the nusinersen and BSC were assumed to have equal survival data.	Same as the company submission, however the most recent UK general population mortality estimates (2021-23) ⁴² were used.	6.3.4.9
Discontinuation	Treatment discontinuation for nusinersen based on MAA ¹⁸ data	Same as company submission, however most recently updated MAA ¹⁸ data was used.	6.3.4.10
Health related quality of life	Health state utility values from HST24 ¹⁶ , and it was assumed that disease modifying therapy increases utility by 10%	Same as company submission, however exploratory analyses including impact of bulbar dysfunction using data from Roche submission ⁴⁴ , utilities used in Roche base-case model ⁴⁴ , and utilities from SUNFISH ⁴⁸ used in Roche model was conducted.	6.3.4.6

Input	Biogen value	EAG changes	Section
Carer health related quality of life	Carer utility increments from TA755 ³ were considered in the base-case analysis	Carer utility from TA755 ³ was not considered in the base-case analysis; however, its impact was assessed in the scenario analyses using utilities from Lo et al, 2022 ⁷¹ as they were more recent UK data.	6.3.2.7
Health care resource utilisation	Health state costs informed by HST24 ¹⁶ , and TA755 ³	Same as the company approach; however, the costs were inflated to the most recent price year.	6.3.4.7
*After the treatment effect period, patients are assumed to maintain the motor milestones achieved to that point and are at risk of losing motor milestones but cannot gain higher motor milestones after this period. Abbreviations: BSC = best supportive care; MAA = Managed Access Agreement; NICE = National Institute for Health and Care Excellence; TA = technology appraisal; HST = highly specialised technology.			

12.2.2 Risdiplam using Roche models

12.2.2.1 Presymptomatic population

The key changes made to the Roche presymptomatic model is summarised in Table 82.

Table 82: Changes made by the EAG to the Roche presymptomatic model

Input	Roche base-case	EAG changes	Section
Decision problem	Risdiplam versus OA; Risdiplam versus nusinersen	Risdiplam versus BSC. Scenario analysis: Risdiplam versus OA; Risdiplam versus nusinersen	7.3.2.1
Time horizon (years)	██████	Lifetime (100 years)	7.3.2.1
Model state transitions	Risdiplam: based on RAINBOWFISH ⁵⁷	Risdiplam: based on RAINBOWFISH ⁵⁷ ; BSC based on internal natural history data.	7.3.2.1.2
Relative effectiveness	Cost-comparison analysis.	Scenario analysis: CUA for risdiplam versus OA and risdiplam versus nusinersen assuming equivalence on average. CUA for risdiplam versus nusinersen based on results from the naïve comparison	7.3.2.5
Treatment effect duration*	After 10 years receiving DMTs only maintained or improved the motor milestones achieved.	Assumption of long-term risk of losing motor milestones based on Wadman et al. ³⁹ Relative risk of decline for risdiplam based on average treatment estimates from the Type 1 and Type 2/3 models. Assumption of 72 months of treatment effect duration for risdiplam before long-term decline, and 15 months for BSC	7.3.2.5
Survival	General UK population	OS for sitting without support, not sitting, and permanent ventilation from HST24 ¹⁶	7.3.2.9
Discontinuation	No discontinuation assumed across DMTs.	Same as company submission.	7.3.2.10
Health related quality of life	Based on TA755. ³	Same approach as HST24 ¹⁶ , Assumption that DMT increases utility by 10%. Approach to adjust utility values for age and gender updated to the latest NICE approach.	7.3.2.6

Input	Roche base-case	EAG changes	Section
Adverse events	No treatment-related adverse events. Non-permanent respiratory support and bulbar dysfunction assumed as disease-related events for BSC patients using internal data from a natural history study by Roche.	Assumption that patient reported health-related quality of life for SMA includes the impact of disease-related events to avoid double-counting events in the BSC arm.	7.3.2.8
Carer health related quality of life	Base-case analysis combined the impact on patients and informal carers. Carer utilities from TA588. ²	Base-case analysis focused on patient utilities only, scenario analyses include the impact on both patients and informal carers; using carer utilities from Lo et al, 2022. ⁷¹ as they were more recent UK data	7.3.2.6
Health care resource utilisation	Based on an expert opinion elicitation exercise from Roche.	Same approach as HST24 ¹⁶ and TA755. ³	7.3.2.7
*After the treatment effect period, patients are assumed to maintain the motor milestones achieved to that point and are at risk of losing motor milestones but cannot gain higher motor milestones after this period. Abbreviations: BSC = best supportive care; MAA = Managed Access Agreement; NICE = National Institute for Health and Care Excellence; TA = technology appraisal; HST = highly specialised technology.			

12.2.2.2 Type 1 population

The key changes made to the Roche type 1 model are summarised in Table 83.

Table 83: Changes made by the EAG to the Roche type 1 model

Input	Roche base-case	EAG changes	Section
Decision problem	Risdiplam versus OA; risdiplam versus nusinersen; risdiplam versus BSC.	Risdiplam versus BSC. Scenario analyses: risdiplam versus OA; risdiplam versus nusinersen.	7.3.3.1
Time horizon (years)	██████	Lifetime (100 years).	7.3.3.1
Model state transitions	Risdiplam: based on FIREFISH. ⁵⁶	Same as company submission.	7.3.3.1.2
Relative effectiveness	Internal results using an unanchored MAIC for risdiplam with nusinersen and BSC using results from ENDEAR ²⁷ , and risdiplam with OA using results from STRIVE-EU. ⁶⁵	BSC: based on Ribero et al. results for uMAIC between FIREFISH ⁵⁶ and ENDEAR. ²⁷ Scenario analyses: OA based on internal STRIVE-EU ⁶⁵ uMAIC results; nusinersen based on Ribero et al. ⁶⁴ results.	7.3.3.5
Treatment effect duration*	After 5.5 years receiving DMTs only maintained or improved the motor milestones achieved.	Risdiplam: 60 months; BSC: 12 months. BSC long-term risk of decline based on Wadman et al. ³⁹ after this period. Relative risk for risdiplam based on HINE-2 motor milestone response results from Ribero et al. Scenario analysis: OA and nusinersen assumption of 60 months, relative risk assumed the same for all DMTs.	7.3.3.5
Survival	OS: exponential; EFS: exponential. OS from FIREFISH ⁵⁶ informed survival for "not sitting" and "sitting" states only.	FIREFISH ⁵⁶ survival adjusted by General UK population mortality over the long term. Mortality at permanent ventilation assumed the same as mortality under BSC across all DMTs.	7.3.3.9
Discontinuation	No discontinuation assumed across DMTs.	Same as company submission.	7.3.3.10
Health related quality of life	Based on TA755. ³	Same approach as HST24 ¹⁶ , assumption that DMT increases utility by 10%. Approach to adjust utility values for age and gender updated	7.3.3.6

Input	Roche base-case	EAG changes	Section
		to the latest NICE approach.	
Adverse events	No treatment-related adverse events. Non-permanent respiratory support, permanent ventilation, and bulbar dysfunction assumed as disease-related events using additional data from the literature.	Assumption that patient reported health-related quality of life for SMA includes the impact of disease-related events to avoid double-counting events.	7.3.3.8
Carer health related quality of life	Base-case analysis combined the impact on patients and informal carers. Carer utilities from TA588. ²	Base-case analysis focused on patient utilities only, scenario analyses include the impact on both patients and informal carers; using carer utilities from as they were more recent UK data	7.3.2.6
Health care resource utilisation	Based on an expert opinion elicitation exercise from Roche.	Same approach as HST24 ¹⁶ and TA755. ³	7.3.3.7
*After the treatment effect period, patients are assumed to maintain the motor milestones achieved to that point and are at risk of losing motor milestones but cannot gain higher motor milestones after this period. Abbreviations: BSC = best supportive care; MAA = Managed Access Agreement; NICE = National Institute for Health and Care Excellence; TA = technology appraisal; HST = highly specialised technology.			

12.2.2.3 Type 2/3 population

The key changes made to the Roche type 2/3 model are summarised in Table 84.

Table 84: Changes made by the EAG to the Roche type 2/3 model

Input	Roche base-case	EAG changes	Section
Decision problem	Risdiplam versus nusinersen; risdiplam versus BSC.	Risdiplam versus BSC. Scenario analyses: risdiplam versus nusinersen.	7.3.4.1
Time horizon (years)	██████	Lifetime (90 years).	7.3.4.1
Model state transitions	Risdiplam: based on SUNFISH ⁵³ risdiplam arm (excluding Asian population)	Same as company submission.	7.3.4.1.1
Relative effectiveness	Risdiplam: based on SUNFISH ⁵³ control arm (excluding Asian population)	Same as company submission. Scenario analysis: nusinersen based on CHERISH ²⁸ uMAIC RULM responders OR (Bucher ITC) published in Ribero et al. (2022) ⁶⁴	7.3.4.5
Treatment effect duration*	After 60 months receiving DMTs patients only maintained or improved the motor milestones achieved.	Risdiplam: 96 months; BSC: 15 months. BSC long-term risk of decline based on Wadman et al. ³⁹ after this period. Relative risk for risdiplam based on probability of stabilisation in SUNFISH from Oskuoi et al. 2023. ⁴⁸ Scenario analysis: nusinersen assumption of 96 months, relative risk assumed the same for all DMTs.	7.3.4.5
Survival	Survival curves from the systematic literature review digitised and pooled together applied to type 2 patients at "not sitting" and "sitting (with and without support)". For type 3 the company assumed equivalent survival to the general population. Assumption of a hazard ratio of 0.75 in OS for risdiplam and nusinersen compared to BSC.	OS for "not sitting" and "sitting (with and without support)" from HST24. General UK population mortality applied to "standing" and "walking". No OS difference between DMTs and BSC, survival gains directly dependent on disease severity improvements from therapy.	7.3.4.9
Discontinuation	No discontinuation assumed across DMTs.	Same as company submission.	7.3.4.10

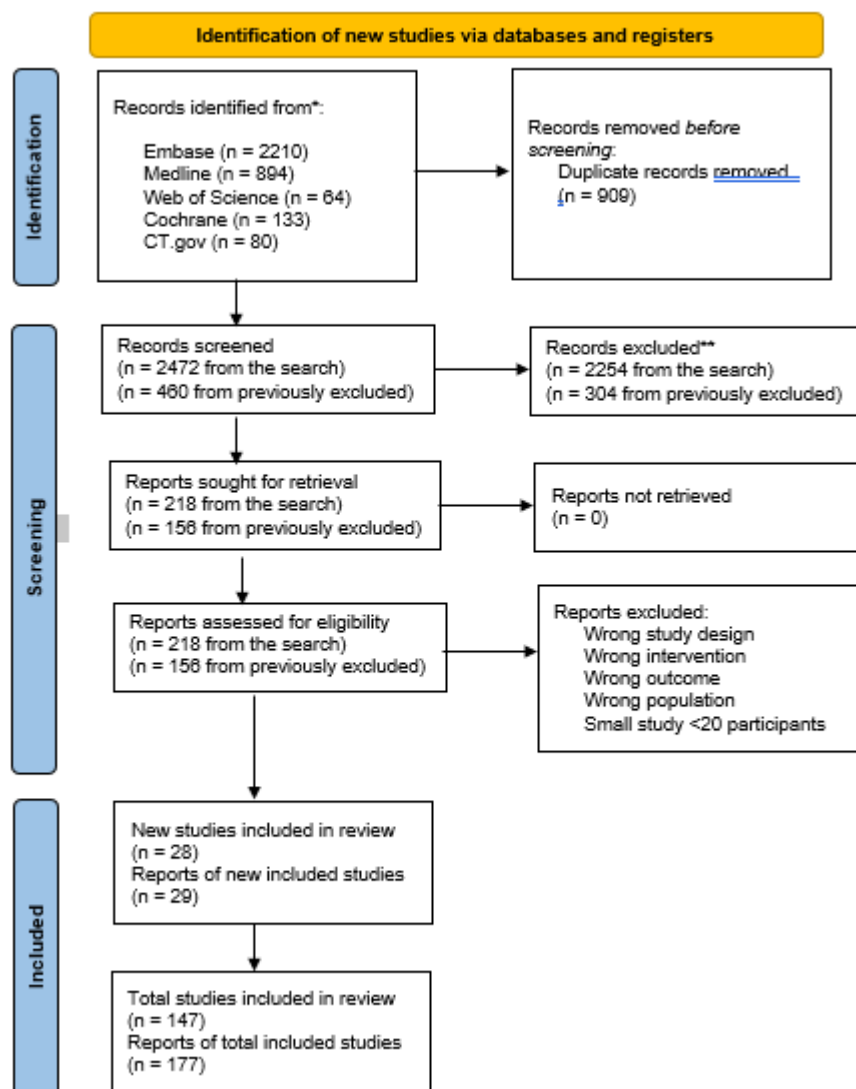
Input	Roche base-case	EAG changes	Section
Health related quality of life	Vignette study from Lloyd et al. 2019 ⁶⁷	Same approach as HST24 ¹⁶ , assumption that DMT increases utility by 10%. Approach to adjust utility values for age and gender updated to the latest NICE approach.	7.3.4.6
Adverse events	No treatment-related adverse events. Non-permanent respiratory support, permanent ventilation, and bulbar dysfunction assumed as disease-related events using additional data on disease history from Roche.	Assumption that patient reported health-related quality of life for SMA includes the impact of disease-related events to avoid double-counting events. Scenario analysis explicitly modelled the impact of bulbar dysfunction for type 2 and 3 patients.	7.3.4.8
Carer health related quality of life	Base-case analysis combined the impact on patients and informal carers. Carer utilities from TA588. ²	Base-case analysis focused on patient utilities only, scenario analyses include the impact on both patients and informal carers; using carer utilities from Lo et al, 2022. ⁷¹ as they were more recent UK data	7.3.2.6
Health care resource utilisation	Based on an expert opinion elicitation exercise from Roche.	Same approach as HST24 ¹⁶ and TA755. ³	7.3.4.7
*After the treatment effect period, patients are assumed to maintain the motor milestones achieved to that point and are at risk of losing motor milestones but cannot gain higher motor milestones after this period. Abbreviations: BSC = best supportive care; MAA = Managed Access Agreement; NICE = National Institute for Health and Care Excellence; TA = technology appraisal; HST = highly specialised technology.			

13 Clinical effectiveness results

The results of the update of the EAG SLR are presented below. These results should be read in the context of the qualitative analysis exploring experiences of those living with SMA, their carers and wider network of family and friends, as well as their experiences of treatment. The qualitative analyses related to the clinical effectiveness can be found in Section 13.5.

A total of 2932 records from the update searches and from the list of previously excluded studies were retrieved for screening, of which 374 were selected for full text review. We included 29 new studies, reported in 30 references. Newly published data from previously included studies, or data that had previously been excluded due to publication type, were added from 51 references. A total of 154 studies reported in 185 reports are reported in this review update.

Figure 32: PRISMA diagram for updated clinical systematic literature review



13.1 Characteristics of all evidence/data for each drug

13.1.1 Nusinersen

Selected references are given here in the text; please see Appendix 4 (Section 19.4) for full table of included studies with full references.

A total of 130 studies in 168 reports evaluating the effectiveness of nusinersen were included, of which 22 reports were new in the update,⁹⁸⁻¹¹⁹ and two were updated with newly published data (NURTURE, SHINE).^{30,120}

Three studies were RCTs (CHERISH, EMBRACE, ENDEAR)²⁷⁻²⁹ and eight had a controlled design of which four compared to treatment-naïve patients, two compared to natural history, and two recruited health control patients.^{99,115,121-126} The rest were single-arm studies (appendix 4).

Studies were conducted across the world: in Europe (n = 73 of which 6 in the UK; TA588 was listed as included in the previous review);^{2,108,109,115,127,128} Asia (n = 18); North America (n = 10); Middle East (n = 4); Australia (n = 3); and South America (n = 2). Seventeen studies took place internationally (including NURTURE, CHERISH, ENDEAR, SHINE), and location was unclear or not reported in three studies.

One study included only presymptomatic patients.¹¹⁴ Eighteen studies focused on patients with type 1 SMA.^{27,103,108,109,115,127-139} Two studies each recruited only patients with type 2^{140,141} or type 3^{142,143} respectively. SMA type was not reported in five studies.^{137,144-147} The rest of the studies included people with different types of SMA.

13.1.2 Risdiplam

A total of 13 studies evaluating the effectiveness of risdiplam were included, three of which were new in the update,¹⁴⁸⁻¹⁵⁰ and three of which were updated with newly published data (SUNFISH, FIREFISH and RAINBOWFISH).^{47,54,57} One was a randomised controlled trial (SUNFISH),⁴⁷ whilst the rest were single arm studies. Five studies were international,^{47,54,57,62,151} two were from each of the USA^{148,152} and Germany,^{153,154} and one came from each of China,¹⁵⁰ Croatia,¹⁵⁵ Spain¹⁴⁹ and the UK.¹⁵⁶ One study included presymptomatic patients only (RAINBOWFISH),⁵⁷ one included patients with type 1 SMA only (FIREFISH),⁵⁴ one included type 2 patients only,¹⁴⁹ and the rest included multiple SMA types (including SUNFISH with types 2 and 3)⁴⁷ or were not reported.^{62,148,150-155}

13.1.3 Mixed interventions

The evidence base for studies that included patients taking more than one treatment comprised one non-randomised controlled study¹⁵⁷ and three single-arm studies.¹⁵⁸⁻¹⁶⁰

13.2 Critical appraisal results (where applied)

13.2.1 Nusinersen

Three randomised controlled trials (RCTs) were assessed using the Cochrane risk of bias tool (ROB 2.0): CHERISH,²⁸ ENDEAR,²⁷ and EMBRACE.²⁹ All three trials were judged overall to have some concerns. A summary of all RoB 2.0 assessments is presented in Table 85.

For the domain “bias arising from the randomisation process”, studies were rated as having some concerns due to imbalances in several prognostic factors between groups, including disease symptoms (ENDEAR), disease duration and a motor milestone (ability to walk with

support) (CHERISH), and age at first dose and SMN2 copy numbers (EMBRACE) (> 5% or 5-point difference in mean/ median value between the intervention and control groups). These differences between groups were not necessarily incompatible with chance, therefore the studies were not rated as being at high risk of bias for this domain.

All three trials were rated as being at low risk of bias for the domain 'effect of assignment to intervention'. It should be noted that trial personnel delivering the intervention were not blinded to each participant's allocation status. However, patients, parents/carers and outcome assessors were blinded. Co-interventions may also have been delivered to treat adverse effects of the intervention. However, this was in line with the trial protocol for each study and this isn't marked down for in the RoB 2.0 guidance.

For the domain 'missing outcome data', both ENDEAR and CHERISH were judged to have some concerns, and EMBRACE was judged to be at low risk. For ENDEAR, all randomised participants were included in time-to-event (death or use of permanent assisted ventilation) analyses. However, < 95% of participants were included in analyses of motor response variables. For the CHERISH study, missing data were imputed.

All three studies were rated as being at low risk of bias for 'measurement of the outcome', as outcome measures seemed appropriate. For 'selection of the reported result', all three studies were reported as being at low risk of bias. However, the EAG notes that only interim data were available in the publications, which may mean that the data are immature.

Twenty-four non-randomised controlled studies were assessed using the ROBINS-I V2 tool. None of the studies were judged overall to have low risk of bias; nine were rated as having moderate overall risk of bias^{121,126,137,144,146,159-162} and fifteen were rated as having serious overall risk of bias.^{73,115,120,122,124,131,145,163-170}. A ROBINS-I V2 assessment could not be implemented for one study,¹²⁵ due to inadequately reported methods. A summary of all ROBINS-I V2 assessments is presented in Table 86.

The most common domains for which risk of bias was demonstrated, were "bias due to confounding" and "bias in measurement of the outcome". The former of these domains ("bias due to confounding") was rated moderate in 10 studies^{121,124,126,137,146,159,161-163,169} and serious in 10 studies.^{73,115,122,131,144}{Schneider, 2021 #1425,145,164,165,168,170} The latter domain ("bias in measurement of the outcome") was rated as moderate in 20 studies^{73,121,124,126,131,137,144,146,159-170} and serious in one study.¹²⁰

Table 85: Risk of bias assessments of nusinersen RCTs

Study ID	Study design	Overall RoB rating	Bias arising from the randomisation process	Effect of assignment to intervention	Missing outcome data	Measurement of the outcome	Selection of the reported result
ENDEAR²⁷	Parallel-group RCT	High	Some concerns	Low	High	Low	Low
CHERISH²⁸	Parallel-group RCT	High	Some concerns	Low	High	Low	Low
EMBRACE²⁹	Parallel-group RCT	Some concerns	Some concerns	Low	Low	Low	Low
Abbreviations: RCT = randomised controlled trial; RoB = risk of bias							

Table 86: Risk of bias of non-randomised controlled studies of nusinersen (incorporating Table 8 from original review)

Author and year	Study design	Overall RoB rating	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Alruthia 2021	Cross sectional Questionnaire	Moderate	Moderate	Low	Moderate	Low	Low	Moderate	Low
Alves 2021	Longitudinal cohort study	Serious	Moderate	Low	Serious	Low	Low	Moderate	Serious

Author and year	Study design	Overall RoB rating	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Chiriboga 2016	Open-label, escalating dose phase 1 study	Serious	Serious	Low	Low	Low	Low	Moderate	Low
Duan 2022*	Non-randomised observational trial	Moderate	Moderate	Moderate	Low	Low	Low	Moderate	Moderate
de la Banda 2020	Prospective study	Serious	Serious	Low	Low	Low	Low	Moderate	Low
Finkel 2021	Phase 2, open-label, multicentre, dose-escalation clinical trial	Serious	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate
Freigang 2021b*	Prospective, multicentre observational study	Moderate	Moderate	Low	Low	Low	Low	Moderate	Low
Kroksmark 2023	Prospective study	Serious	Low	Low	Moderate	Low	Low	Moderate	Low

Author and year	Study design	Overall RoB rating	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Lee 2022	Retrospective study	Moderate	NI	Low	Low	Low	Low	Moderate	Moderate
Li 2024*	Single-centre retrospective case-control study	Serious	Moderate	Low	Serious	Low	Low	Moderate	Moderate
Mirea 2021	Observational study	Moderate	NI	Low	Low	Low	Low	Moderate	Low
Mirea 2022	Retrospective observational study	Serious	Moderate	Low	Low	Low	Low	Moderate	Serious
Pane 2022	Real-world data	Serious	Serious	Low	Low	Low	Low	Moderate	Low
Pechmann 2023	SMARtCARE registry of longitudinal data used	Moderate	Moderate	Low	Low	Moderate	Low	Moderate	Moderate
Pandey 2025*	Prospective cohort	Serious	Serious	Moderate	Moderate	Low	Low	Low	Low
Rich 2022	Retrospective analysis of	Moderate	Serious	Low	Low	Low	Low	Moderate	Low

Author and year	Study design	Overall RoB rating	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
	samples collected during two trials (NCT04139343 and NCT04591678)								
Schneider 2021	Single-centre cross-sectional and longitudinal study	Serious	Serious	NI	Low	Low	Low	Low	Moderate
SHINE (Dunaway Young 2023)	Uncontrolled Before and After Study/Time Series	Serious	Low	Low	Low	Low	Low	Serious	Serious
Trancho 2024	Observational study	Moderate	Moderate	NI	NI	NI	Low	Moderate	Low
Trucco 2023*	Multicentre cross-sectional prospective study	Moderate	Moderate	Moderate	Low	Low	Low	Moderate	Low
van der Heul 2020	Prospective study	Serious	Serious	Serious	Moderate	Low	Low	Moderate	Low

Author and year	Study design	Overall RoB rating	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Vazquez-Costa 2022	Prospective observational study	Serious	Moderate	Low	Low	Low	Low	Moderate	Serious
Weaver 2021	Observational cohort study	Serious	Serious	Serious	Moderate	Low	Low	Moderate	Low
Weststrate 2021*	Retrospective audit	Serious	Serious	Low	Low	Moderate	Low	Low	Low
*Study added in the update Abbreviations: NI = no information; RoB = risk of bias									

13.2.2 Risk of bias

The SUNFISH RCT⁴⁷ was assessed using the Cochrane RoB 2.0 tool as having some concerns, due to imbalances in motor function between intervention and control group at baseline as shown in Table 87. For the domain 'bias arising from the randomisation process', SUNFISH was rated as having some concerns; although the reported randomisation process was robust, there were nevertheless some imbalances at baseline in motor scores. For the rest of the domains the SUNFISH trial was judged to be at low risk of bias.

Table 87: Risk of bias assessment of risdiplam RCT

Study ID	Study design	Overall RoB rating	Bias arising from the randomisation process	Effect of assignment to intervention	Missing outcome data	Measurement of the outcome	Selection of the reported result
SUNFISH ⁴⁷	Randomised parallel-group trial	Some concerns	Some concerns	Low	Low	Low	Low

Abbreviations: RCT = randomised controlled trial; RoB = risk of bias

13.2.3 Risdiplam versus nusinersen

One controlled study,¹⁵⁷ which compared the effectiveness of risdiplam and nusinersen, was critically appraised using the ROBINS-I V2 tool. As shown in Table 88, the study was rated as having serious risk of bias overall due to having multiple (n=4) domains rated as moderate risk of bias.

Table 88: Risk of bias of non-randomised controlled study of risdiplam compared to nusinersen

Author and year	Study design	Overall RoB rating	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Ashrafi, 2024	Prospective cohort	Serious	Low	Moderate	Low	Moderate	Moderate	Moderate	Low

13.3 Effectiveness

This section covers outcomes for which data could be included in either the base case models for nusinersen and risdiplam or the scenario analyses, and also outcomes where data could not be modelled. Many outcomes were represented by data which could not be incorporated into the models; many of these were highlighted to the EAG as being important to patients and carers. Additional outcomes which were not in the original scope, but which were highlighted as important by patient and professional groups are included in the updated SLR and represented in the MAA, where data allows. All the effectiveness data should be considered in the context of the qualitative analysis of information provided by patients and professionals.

13.4 Narrative synthesis of all results by outcome incorporating critical appraisal/source as caveats

The narrative synthesis includes all outcomes from the NICE decision problem and the extra outcomes as defined during patient consultation where reported. If an outcome is not reported below, it can be assumed that it was not included in any of the studies for that particular SMA type.

13.4.1 Nusinersen

13.4.1.1 Motor function

The clinical trials reporting data for the effects of nusinersen on motor function were SM201 and NURTURE for patients with presymptomatic SMA, CS3A and ENDEAR for type 1 patients, CS12A and CHERISH for types 2-3 patients, and SHINE which was an open label extension study following the ENDEAR and CHERISH studies for patients with types 1-3 SMA. This updated review contains newly published data for each of these studies, which suggests improved or maintained motor function on average across the spectrum of SMA for each of the outcomes assessed, relative to a control group of before-after observations, for follow-up timepoints of up to 5 years. Some studies reported differences in effectiveness between population sub-groups, in relation to age (e.g., one study reported greater increases in CHOP INTEND scores amongst non-sitters with 2 copies of SMN2 who were aged ≤ 9 months compared to those aged > 9 months¹⁷¹). Another study reported significant increases in type 1 and 2 patients but not type 3 patients.¹⁷² A third study reported that higher dosage of nusinersen was associated with greater improvements in CHOP INTEND scores.¹⁷³

13.4.1.1.1 WHO motor milestones

SLR evidence

Presymptomatic

Two records,^{30,174} reported in the earlier review, reported data for the effects of nusinersen on WHO MM assessments in presymptomatic patients. In NURTURE, patients were able to sit without support and all children who achieved milestones retained them at the last visit.³⁰ Additionally, 5/7 patients were able to sit independently, 1/5 was able to stand unaided and one was able to walk with support. Amongst younger patients, two were able to stand with support (SM201).¹⁷⁴ The updated review identified one further uncontrolled study (i.e., a study without an independent control group), which aimed to assess the impact of screening on early treatment of SMA.¹¹⁴ The study reported that asymptomatic patients who received early treatment, via nusinersen, achieved timely acquisition of WHO MMs.¹¹⁴

New final analysis data from NURTURE further supports the long-term benefit of nusinersen in presymptomatic patients.^{175, 176} At the last study visit (~5 years), all 15 participants with 2 SMN2 copies achieved the WHO motor milestones of sitting without support and standing with assistance. All 10 participants with 3 SMN2 copies achieved all six WHO motor milestones. Among those with 2 SMN2 copies, the majority also achieved hands-and-knees crawling (93%), walking with assistance (93%), standing alone (93%), and walking alone (87%). Importantly, all participants who achieved a milestone during the study retained that milestone at the final assessment.^{175,176}

Type 1

No studies reported WHO motor milestones in type 1 patients.

Types 2 and 3

Two records,^{28,177} reported in the earlier review, included data for the effects of nusinersen on WHO MM in type 2/3 patients. There was an observed 20% gain in at least one motor milestone for those treated with nusinersen, compared to 6% in the control group (CHERISH).²⁸ Additionally, 14.9% of young sitters and 1.3% of older sitters gained the ability to walk independently following treatment. Furthermore, no motor milestones were lost during nusinersen treatment.¹⁷⁷

Multiple types

Two records,^{120,178} included in the earlier review, reported data for the effects of nusinersen on WHO MM in patients with mixed types of SMA. Significant increases¹⁷⁸ and stable or higher milestones in all patients (SHINE)¹²⁰ were observed. Three new uncontrolled studies were identified in this update.^{117,179,180} One study also identified stabilisation or improvement in WHO MM between baseline and follow-up in patients (n = 45).¹⁷⁹ Another study reported that 54 patients gained new motor skills after three years of nusinersen treatment, while two lost a motor ability and one remained stable.¹⁸⁰ Finally, a retrospective assessment of SMA type 1 (n = 8) and 2 (n = 30) patients showed improvements in sitting without support and crawling.¹¹⁷

SMA type not reported

Two studies, reported in the earlier review,^{131,137} assessed patients receiving nusinersen where the SMA type was not reported. One study reported that 1/4 (25%) patients achieved developmental motor milestones in cohort 1 compared to 8/15 53% in cohort 2.¹³¹ In a further study, n=29 (33%) in the younger cohort and n=6 (10.9%) in the older cohort gained the ability to sit independently, and no milestones were lost in any patients.¹³⁷

MAA evidence

Paediatric registry

The data for the WHO MM was updated by the paediatric registry in April 2025 from the original submissions in December 2023. The updated data are presented and discussed for this outcome, as it is more mature than the original report.

Data were presented reporting the number of patients for each SMA type that either maintained or attained motor milestones. Two versions of the data were presented: one of which excluded those with missing data; and another which used linear interpolation for missing data. The MAA data suggests that longer follow-up led to maintenance and improvement for a number of patients (see

Table 89 and Table 90) The registry highlights the significance of these descriptive data compared to natural history. The natural progression of the condition means motor function, as well as respiratory and bulbar function, deteriorates over time. This is especially true for type 1 patients but is also inevitable for type 2/3 patients. As such, stabilisation can be considered a treatment effect and potentially lead to better long-term outcomes and quality of life. In this real-world dataset, where patients were heavily symptomatic and chronically affected by the condition at baseline, there is clear evidence of stabilisation for a number of patients across each SMA type.

Table 89: Nusinersen paediatric registry WHO MM attainment or maintenance of motor milestones

Nusinersen paediatric WHO MM		Time point (n/N)							
Measure	Type	6 months	1 year	1.5 years	2 years	2.5 years	3 years	3.5 years	4 years
Attainment of a motor milestone	1 (EAP)	■	■	■	■	■	■	■	■
Attainment of a motor milestone	1 (Non-EAP)	■	■	■	■	■	■	■	■
Attainment of a motor milestone	2/3 non-sitters	■	■	■	■	■	■	■	■
Attainment of a motor milestone	2/3 sitters	■	■	■	■	■	■	■	■
Attainment of a motor milestone	2/3 walkers	■	■	■	■	■	■	■	■
Attainment or maintenance of a motor milestone	1 (EAP)	■	■	■	■	■	■	■	■
Attainment or maintenance of a motor milestone	1 (Non-EAP)	■	■	■	■	■	■	■	■
Attainment or maintenance of a motor milestone	2/3 non-sitters	■	■	■	■	■	■	■	■
Attainment or maintenance of a motor milestone	2/3 sitters	■	■	■	■	■	■	■	■
Attainment or maintenance of a motor milestone	2/3 walkers	■	■	■	■	■	■	■	■
Abbreviations: WHO MM = World Health Organisation Motor Milestones; N = overall number of patients; n = number of patients achieving; MM = Motor Milestone; EAP = Expanded Access Programme									

Table 90: Nusinersen paediatric registry WHO MM attainment or maintenance of motor milestones with linear interpolation for missing data.

Nusinersen paediatric WHO MM	Time point: interpolation used (n/N)

Measure	Type	6 months	1 year	1.5 years	2 years	2.5 years	3 years	3.5 years	4 years
Attainment of a motor milestone	1 (EAP)	■	■	■	■	■	■	■	■
Attainment of a motor milestone	1 (Non-EAP)	■	■	■	■	■	■	■	■
Attainment of a motor milestone	2/3 non-sitters	■	■	■	■	■	■	■	■
Attainment of a motor milestone	2/3 sitters	■	■	■	■	■	■	■	■
Attainment of a motor milestone	2/3 walkers	■	■	■	■	■	■	■	■
Attainment or maintenance of a motor milestone	1 (EAP)	■	■	■	■	■	■	■	■
Attainment or maintenance of a motor milestone	1 (Non-EAP)	■	■	■	■	■	■	■	■
Attainment or maintenance of a motor milestone	2/3 non-sitters	■	■	■	■	■	■	■	■
Attainment or maintenance of a motor milestone	2/3 sitters	■	■	■	■	■	■	■	■
Attainment or maintenance of a motor milestone	2/3 walkers	■	■	■	■	■	■	■	■
Abbreviations: WHO MM = World Health Organisation Motor Milestones; N = overall number of patients; n = number of patients achieving; MM = Motor Milestone; EAP = Expanded Access Programme									

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The registry reported data split by type 2/3 non-sitters, sitters, and walkers. Non-sitters had one patient gain a motor function status, becoming a sitter. This patient scored one on the WHO assessment (item 1) on months 18 to 36, increasing from WHO item 0 to 1 at 18 months. In the sitters, five patients declined in motor function status (became a non-sitter). Three patients gained WHO motor function status, becoming a walker. Forty-four sitter patients remained a sitter. The five patients who lost WHO motor function (became a non-sitter), scored 1 on WHO scale and dropped to 0 at the time of loss of motor function, or had missing data. Patients who gained WHO walker motor function scored 3-5 on previous visits as a sitter before gaining walker status (score = 6). For the walkers, three patients lost motor function status (became a sitter). Forty-six patients remained as walkers (for a breakdown of motor milestones at follow-up see Table 91).

The registry stated that the results are similar to natural history in the adult SMA population. They show maintenance with limited transition between functional groups. Overall, four patients gained a motor milestone, eight lost one, and 105 were stable throughout the study period. The stability captured on the WHO motor scale demonstrates the known stability of this group. However, it is important to note the lack of sensitivity of this scale; it does not capture important subtle changes. For example, the sitters group can score 1-5 on the WHO motor scale and not change classification. Therefore, a change from sitter to walker implies a significant change in their motor function, which was experienced by three patients.

13.4.1.1.2 CHOP-INTEND

SLR evidence

Presymptomatic

Two records, reported in the earlier review,^{30,174} included data for the effects of nusinersen using CHOP INTEND assessments in presymptomatic patients. Improvements were seen on CHOP INTEND following nusinersen, with mean scores of 62.1 for patients with two copies of SMN2 and 63.4 for patients with three copies of SMN2 in the NURTURE trial,³⁰ while 7/18 patients achieved maximum scores in SM201.¹⁷⁴

New data from NURTURE provides additional long-term evidence of CHOP INTEND outcomes in presymptomatic patients treated with nusinersen.^{175,176} At baseline, CHOP INTEND scores ranged from 25 to 60, with a median of 50.0 overall (45.0 in participants with two SMN2 copies and 53.5 in those with three copies). All 25 participants in the ITT population demonstrated improvement from baseline to the last visit (up to Day 2891). Twelve of 15 participants (80%) with two SMN2 copies and all 10 participants (100%) with three SMN2 copies achieved the maximum score of 64, after which assessments were discontinued per protocol. At the final visit, mean CHOP INTEND scores were 63.3 for the 2-copy group and 64.0 for the 3-copy group. These findings were supported by longitudinal plots showing consistent increases over time.^{175,176}

Type 1

Fifteen records, seven of which were reported in the earlier review,^{27,133-136,159,181} examined the effect of nusinersen on CHOP INTEND in Type 1 patients. These seven records reported data from the ENDEAR trial. Overall, scores on CHOP INTEND increased amongst the majority of patients but some also showed stabilisation of scores.^{135,136,159} Further results from a newly identified uncontrolled study¹³¹ extracted for this review update, found that, at the final visit response rates were 52/73 (71%) vs 1/37 (3%) ($P < .001$; ≥ 4 -point increase), respectively for the intervention and control groups.

Nine uncontrolled studies^{98,103,108,109,113,117,118,125,182} were newly included in this review update.

Three studies^{103,108,109} reported data from EAPs. One of these studies¹⁰³ reported median progress on the CHOP INTEND scale was 4 points at 6 months ($n=17$). In another study,¹⁰⁸ it was reported that 75% of the patients showed an improvement of the CHOP Intend total score after the 4th or 5th injection. The third study¹⁰⁹ reported that, from baseline to follow-up, most patients showed improved CHOP INTEND scores (between 1-17 points, with a mean of 36/64 at the 5th injection). Additionally, few patients remained stable and one dropped from 52 at baseline to 46 at the 5th injection due to limited mobility secondary to a bone fracture, but scored 58 after the 4th injection.

Of the remaining studies, one¹⁸² reported that CHOP INTEND scores increased from 25.6 ± 15.4 at baseline to 33.0 ± 23.4 at follow-up amongst $n=8$ participants with type 1 SMA. Another study¹¹³ found that during the first year of treatment, there was a significant increase in CHOP INTEND score in type 1 patients. Results from a different study¹²⁵ suggested that, for type 1 patients, CHOP INTEND scores increased 14.8 points per year ($n=29$; median follow-up 12 months, range 7.8-15.0 months). Additionally, another study⁹⁸ reported that CHOP INTEND scores in SMA type 1 patients increased significantly after loading treatment compared to baseline, and this improvement progressively increased with subsequent doses. Another study¹¹⁷ reported changes in CHOP INTEND scores amongst in six patients with type 1 SMA

from mean 19.5 ± 11.9 at baseline to mean 20.5 ± 12.1 at day 63 ($P = 0.416$). Finally, a different study¹¹⁸ reported median CHOP INTEND scores of 23 (range 0-38) at baseline and 41 (range 3-64) at follow-up (median duration 37.7 months) amongst nusinersen recipients.

Types 2 and 3

One study¹³³ reported data for the effects of nusinersen on CHOP INTEND in type 2 and type 3 patients. As reported in the earlier review, the results showed an overall mean increase of 2.37 points.

Multiple types

Twenty-four records reported data for the effects of nusinersen on mixed types of SMA. Twenty of these studies^{120,167,172,173,178,182-196} were included in the earlier review. Four additional, uncontrolled studies were identified in this review update.^{98,106,117,171}

One study,¹²⁰ from the Warwick review, reported results from the SHINE trial, which suggested increased CHOP INTEND scores amongst patients treated with nusinersen. Another study,¹⁷¹ identified in this review update, reported data from the RESPOND trial, showing that, at day 183 following nusinersen treatment, there were mean changes (SD) in CHOP INTEND scores of $+6.7 \pm 6.76$ for people aged ≤ 9 months with 2 copies of SMN2 and $+0.6 \pm 5.50$ for patients aged > 9 months with 2 SMN2 copies. Among non-sitters, the mean changes were $+6.7 \pm 6.76$ for people aged ≤ 9 months with 2 copies of SMN2 and $+3.6 \pm 3.91$ for those aged > 9 months with 2 copies of SMN2. Additional results reported in the earlier review were as follows. Two studies showed varied results, with one suggesting unclear effectiveness¹⁸⁶ and the other suggesting 67% patients remained clinically stable.¹⁸⁹ Patients receiving higher doses of nusinersen showed higher increases in CHOP INTEND scores,¹⁷³ scores for non-sitters increased by six points,¹⁹⁶ and significant increases were observed in type 1 and 2 patients but not type 3 patients.¹⁷² The remaining studies observed increased CHOP INTEND scores.^{167,178,182,184,185,187,188,190-195}

The results from an additional study¹⁰⁶ included in this review update showed that 23 patients (85.2%) (denominator not reported) demonstrated the clinical effectiveness of nusinersen based on the CHOP INTEND score after receiving treatment. Of these, seven were type 1 SMA patients (58.3%), 15 were type 2 SMA patients (57.7%), and 1 was a type 3 SMA patient (25.0%) who demonstrated clinical improvement.

Unreported type

Four studies examined CHOP INTEND in patients with unreported SMA type following nusinersen.^{127,137,183,197} As reported in the earlier review, all four studies showed an improvement.

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report.

Two MMRMs were conducted: one assessing the whole type 1 cohort and the other a sensitivity analysis for those who were non-EAP and EAP type 1 patients. Of the original covariates, weight was not statistically significant. Coupled with its poor data collection, leading to reduced sample size, the analysis without weight as a covariate was preferred.

In the first model, there was a statistically significant interaction between visit and CHOP INTEND score. For the sensitivity analysis, non-EAP and EAP categorisation also significantly interacted with visit. The results suggested a consistent increase in CHOP INTEND scores from baseline up to four years, with the majority showing statistically significant improvements. The sample size reduced from 54 patients at baseline to three patients at 4 years follow-up within the main analysis.

Adult registry

This outcome is not applicable for adult patients as CHOP INTEND is used for those aged 1-38 months.¹⁹⁸

13.4.1.1.3 HINE-2

SLR evidence

Presymptomatic

One study, which was included in the earlier review,¹⁷⁴ reported data for the effects of nusinersen on HINE-2 assessments in presymptomatic patients. As reported in the original review, all patients had age-appropriate motor development and 5/5 patients developed additional milestones at day 302 following nusinersen treatment. At the last study visit, 13/18 patients had achieved the maximum score for this assessment in the SM201 trial.

New data from NURTURE provided updated long-term HINE-2 data for presymptomatic patients treated with nusinersen.^{175,176} All 25 participants achieved the maximum level for head control, sitting, voluntary grasp, kicking, and rolling. Eleven of 15 participants (73%) with two SMN2 copies and all 10 participants (100%) with three SMN2 copies achieved the maximum level for crawling and standing. Additionally, 10 of 15 participants (67%) with two SMN2 copies and all participants with three SMN2 copies achieved the maximum level for walking. At the final assessment, all participants with three SMN2 copies reached the maximum HINE-2 total score of 26. The mean total score in the two-copy group was 23.9 (range: 16–26).^{175,176}

Type 1

Seven records, four of which were included in the earlier review,^{27,134-136} and three newly identified records reporting data from uncontrolled studies,^{103,109,182} examined motor function using HINE-2/HINE in type 1 patients following nusinersen treatment.

One record²⁷ reported data from the ENDEAR trial. The results from this study indicated that, in the interim analysis, a significantly higher percentage of infants in the nusinersen group than in the control group had a motor-milestone response (21 of 51 infants [41%] vs. 0 of 27 [0%], $P < 0.001$). Furthermore, in the final analysis, a significantly higher percentage of infants in the nusinersen group than in the control group had a motor-milestone response (37 of 73 infants (51%) vs. 0 of 37 (0%)).

Among the other studies reported in the earlier review, the majority of patients remained stable,¹³⁴ 21/68 patients reached the ability to sit,¹³⁵ and 44.5% patients improved from baseline to 48 months.¹³⁶

Results extracted for the updated review from a newly identified study¹⁰³ showed that median progress on the modified HINE-2 score was 1.5 points after 6 months of treatment ($P < 0.0001$) regardless of SMN2 copy number. In the same study, patients who scored ≥ 2 points on the modified HINE-2 at baseline presented with an improvement two times higher than patients

scoring < 2, although the difference did not reach statistical significance. Another newly identified study reported an increase in HINE score from 2.5 ± 3.1 to 5.5 ± 7.1 in eight type 1 patients. The follow-up timeframe was unclear and could be either 6 or 12 months.¹⁸² The remaining newly identified study reported an improvement of at least 2 points in 9/17 patients at the 5th injection with no cases of motor regression.¹⁰⁹

Multiple types

Twelve records reported data that examined HINE-2 in patients with multiple types of SMA following nusinersen.^{29,107,120,171,178,179,182,184,186,199-201} Eight of these^{120,178,182,184,186,199-201} were reported in the earlier review.

One newly identified record reported data from the EMBRACE trial (a controlled study; rated 'some concerns' using the ROB 2.0),²⁹ showed that the percentages of HINE-2 responders in the nusinersen and sham group were 78% vs 0%, respectively. Results from the RESPOND trial of patients who previously received OA, reported by two records and included in the earlier review^{107,171} showed that the mean change in HINE-2 score at day 183 was 8.6 in group 1 (patients with two SMN2 copies, aged ≤ 9 months) and 13.5 in group 2 (patients with two SMN2 copies, aged > 9 months). Another record from the earlier review¹⁷⁹ reported results from the PANDA trial, showing that mean change from baseline in HINE-2 scores were 7.3 and 3.2 for the infantile-onset and later-onset groups at day 423. Furthermore, the proportion of HINE-2 responders was seven of nine (77.8%) evaluable participants in the infantile-onset SMA subgroup and 30/32 (93.8%) evaluable participants in the later-onset SMA subgroup.

Unreported type

Three records,^{129,131,197} which were included in the earlier review, reported data that examined HINE-2 following nusinersen treatment in patients where SMA type was not reported. One of the studies reported that, in patients with two copies of SMN2, 63% showed incremental improvements in scores.¹³¹ Additionally, sitters had more improvement than non-sitters (3 vs 1 point increase).¹²⁹ Finally, amongst patients with two copies of SMN2, all showed improvement, eight presymptomatic patients remained symptom free, and, amongst those with three copies of SMN2, one patient had delayed milestones, whilst all other patients remained asymptomatic with normal milestones.¹⁹⁷ One newly identified uncontrolled study¹⁰⁷ reported mean change from baseline to follow-up (day 183) values of 5.4 for patients aged ≤ 9 months with two copies of SMN2, and 5.2 for patients aged > 9 months with two SMN2 copies. Mean scores at day 183 were 8.6 in patients aged ≤ 9 months with two copies of SMN2 and 13.5 for patients aged > 9 months with two SMN2 copies.

MAA evidence

Paediatric registry

The results for this outcome are taken from the updated April 2025 report.

An MMRM was conducted in type 1 patients; weight had missing values and the preferred model did not include weight as it allowed for patient data to be included in the analysis. The interaction between visit and baseline HINE score was statistically significant. The results suggest an improvement in HINE score from baseline ($n = 50$) over the follow-up period, up to four years ($n = 5$). A sensitivity analysis of non-EAP and EAP patients was conducted. The interaction between non-EAP and EAP groups and visit was statistically significant. Both groups showed positive results, with increases in HINE scores from baseline up to 4 years.

Adult registry

This outcome is not applicable for adult patients as HINE is used for those aged 2-24 months.¹⁹⁸

13.4.1.1.4 BSID-III

No evidence for this outcome was identified for any SMA type in the original or updated review for patients treated with nusinersen.

13.4.1.1.5 RHS

SLR evidence

There was no reported evidence for presymptomatic or type 1 patients.

Types 2 and 3

Three records reported data for the effects of nusinersen on motor function assessed using the RHS. One study,²⁰² which was included in the earlier review, reported a significant increase in RHS score at six months but not beyond.²⁰² Two new studies were identified during this review update.^{119,122} The results from one of the newly identified studies,¹²² an RCT (ROB 2.0 rating: serious), showed that the mean RHS score in the nusinersen group increased from 35 (± 18) at baseline to 38.9 (± 19) and 39.9 (± 17) at 6 and 12 months, respectively ($P = 0.001$). In the standard of care (SoC) group, the scores increased from the baseline of 28.8 (± 15) to 29.6 (± 16) and 29.9 (± 17) at 6 and 12 months, respectively ($P = 0.35$). The mean gain in the RHS score over 12 months in the nusinersen group was significantly higher compared to the SoC group ($P = 0.02$). Another uncontrolled study reported results from the NICE SMA evaluation.¹¹⁹ The results showed a mean change of 0.8 ± 4.1 ($P > 0.05$) from baseline to 14 months for 31 participants. Additionally, the number of patients gaining 3 or more points on RHS at 14 months was 8/31 (26%), while the number who lost 3 or more points was 4/31 (13%).

Multiple types

One study,¹⁹² reported in the earlier review, which included people with different types of SMA, showed that following nusinersen treatment, there was no significant increase in RHS score for 12/17 type 3 patients.

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report.

Type 1

RHS is used in type 1 only if the CHOP INTEND ceiling effect is observed, or if a patient has achieved such skills as rolling and sitting (not assessed in CHOP INTEND). Weight was again not a statistically significant predictor and excluded from the analysis. As these patients are originally measured on the CHOP INTEND, a new baseline was created using the RHS. The interaction between visit and the new baseline was significant. The MRMM included 30 patients and there are differences in when the baseline occurred, therefore the registry suggests extreme caution when interpreting the results. The results do suggest a positive impact, with an increase or maintenance (i.e. no statistically significant decreases) in RHS

score up to 2.5 years follow-up from baseline (n = 3). The registry also highlighted that there are no expected milestones in the natural history for this patient population and that the RHS was initially developed for type 2/3 patients. The registry did consider a sensitivity analysis with the non-EAP and EAP groupings. However, due to when the EAP patients received nusinersen (i.e. prior to MAA inclusion), and being a more severely affected group of patients, it was less likely they would achieve a ceiling effect. The groups were therefore not considered comparable and the analyses were not conducted.

Types 2 and 3

An MMRM was conducted in type 2/3 patients for changes in RHS assessments. Similar to CHOP INTEND, weight was not a statistically significant predictor and was removed from the analysis. Additionally, visit and baseline RHS score did not have a significant interaction, which were also removed to simplify the model. There was evidence of an increased RHS score over time from baseline to four years. At baseline there were 96 patients and at four years 11 patients.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The adult registry reported a MRMM for RHS in type 2/3 data for sitters and walkers. For sitters, no statistical significance was observed. However, the numerical trend of improvement suggests potentially positive outcomes for these patients. Potential improvement was suggested but should be interpreted with caution due to lack of data, with only 15 patients available at baseline and six patients with follow-up data at 2.5 years.

Similar results were observed for the walkers. No statistical significance was observed. However, the numerical trend suggests maintenance over the follow-up period, with small improvements in the first 2.5 years and non-statistically significant decreases from 2.5 to 4 years. Data was limited in the longer follow-up periods, with 39 patients available at baseline but only 10 at four years follow-up. Nevertheless, maintenance may be represented in this data, this should be considered a good outcome.

13.4.1.1.6 RULM

SLR evidence

There was no reported evidence for presymptomatic or type 1 patients.

Type 2

One study,¹⁴¹ included in the earlier review, reported a significant increase in RULM scores between baseline and month 12, as well as a significant difference between the number of clinically meaningful improvements between treated and untreated patients.

Another study,¹²⁵ which included a treatment naïve group (risk of bias could not be assessed due to limited information reported) and was identified in this review update, reported that nusinersen-treated type 2 patients had increased RULM scores of 2 points per year (4.8 months follow-up; range 3.3-12.2 months), while treatment-naïve patients, also with type 2 SMA, had decreased RULM scores, by -0.75 points per year.

Type 3

One study,²⁰³ reported in the earlier review, examined RULM in type 3 patients following nusinersen. Increases in scores were found up to 12 months of treatment.

Types 2 and 3

Ten records, seven of which were included in the earlier review,^{28,122,168,177,204-206} and three newly identified uncontrolled studies,^{117,119,207} examined the effects of nusinersen on RULM in patients with types 2-3 SMA.

Results reported in the earlier review are as follows. One record reported results from the CHERISH trial, showing that RULM scores increased by 4.2 points in the nusinersen group and by 0.5 in the control group. A record that was newly included in this review update reported results from the NICE SMA study, in which gains in RULM scores were higher in the nusinersen group (baseline mean 29.0 ± 8.3 ; 12-month mean 31.3 ± 6.6 ; $P = 0.022$) compared to the SoC group (baseline mean 25.7 ± 7.5 ; 12-month mean 26.3 ± 7.2 ; $P = 0.539$).¹²²

Another record from the earlier review reported results from the CS2/12 trial, showing an increase in RULM scores following nusinersen treatment.²⁰⁴ The remaining studies from the earlier review showed a significant increase in RULM scores in type 2 patients, but not in type 3,¹⁶⁸ and an increase in clinically meaningful improvements following nusinersen treatment.^{177,205,206}

Of the remaining (newly identified) studies, one²⁰⁷ reported that there was no statistically significant change in the average RULM score from baseline to the fourth, fifth and sixth treatments. However, a positive trend was observed, with more marked improvements in the non-ambulatory group. A different study¹¹⁹ reported mean changes of 1.4 ± 1.8 ($P = 0.0004$, $n = 29$), 0.9 ± 2.0 ($n = 26$, $P \leq 0.02$) and 1.0 ± 2.4 , ($P \leq 0.02$, $n = 23$) at 15 days, 6 and 14 months, respectively, after nusinersen treatment. At 14 months, 9/23 (39%) gained 2 or more points and 3/23 (13%) lost 2 or more points on the RULM scale. Another study¹¹⁷ reported that mean RULM scores increased from 15.8 ± 8.7 at baseline to 17.6 ± 9.3 at day 63 ($P = 0.004$) amongst 20 patients with type 2 SMA. For people with type 3 SMA, mean RULM scores were 29.3 ± 4.8 at baseline and 32.7 ± 2.7 at day 63 ($P = 0.042$).

Multiple types

Fifteen records reported data from studies that examined RULM in patients with mixed types of SMA following nusinersen treatment. Thirteen of these were included in the earlier review,^{120,169,182,185,190,193,195,196,208-212} while two, uncontrolled studies were newly identified in this review update.^{101,106}

Amongst the records included in the earlier review, one reported results from the SHINE trial, which showed increases in RULM following nusinersen treatment.¹²⁰ One study showed improvement amongst paediatric patients and stabilisation in adult patients²⁰⁹ and one study showed increases in five type 2 patients and decreases in five patients, with increases in two type 3 patients, stabilisation in two patients and decreases in one.¹⁹⁰ Another study showed a decrease of -2.40 points amongst patients who discontinued treatment.²¹⁰ The remaining studies showed increases in RULM scores following nusinersen treatment.^{169,182,185,193,195,196,208,211,212} A further study¹⁸² reported changes in mean RULM scores of 5.0 ± 4.2 at baseline to 10.0 ± 9.9 at follow-up (timescale not reported) in two type 1 SMA patients; mean changes of 10.0 ± 8.6 at baseline to 12.6 ± 9.9 at follow-up in seven type 2 SMA patients; and changes in mean values from 28.6 ± 6.2 baseline to 30.4 ± 5.8 at follow-up in seven type 3 patients.

Amongst the studies that were newly included in this review update, one study¹⁰¹ reported changes in mean RULM scores from baseline (25, n=67) to six months (28, n=47) and 10 months (31, n=38) ($P=0.0000$). The other study¹⁰⁶ found that the numbers of patients in which nusinersen was shown to be clinically effective (improvement shown in at least one outcome measure) were three (25%), 10 (38.5%), and one (25%) for patients with types 1, 2 and 3 SMA, respectively, as well as 14 (51.9%) for the total sample ($P=0.668$). The number of patients who showed clinically meaningful improvement (an increase of ≥ 2 points in the RULM score) following nusinersen treatment were: two (66.67%), 10 (100%) and one (100%), respectively, for patients with types 1, 2 and 3 SMA, with 13 (92.86%) for the total sample ($P=0.139$). The median and interquartile range (IQR) scores after nusinersen treatment were: 2 (1.5, 3.0; n= 12), 5.5 (3.3, 8.8; n= 26), 2 (2.0, 2.0; n= 2) for patients with types 1, 2 and 3 SMA, respectively, and 4 (2.3, 7.5; n=42) for the whole sample ($P=0.086$).

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report.

Type 1

The RULM was developed for patients aged 2.5 years and over who can sit supported or unsupported and have functional use of their upper limbs. Historically, this scale would not have been considered for type 1 patients. However, due to disease modifying therapies, these assessments are beginning to be utilised. Similar to the RHS type 1 analysis, the baseline was adjusted to the new RULM scale from CHOP INTEND. The MRMM, excluding weight, showed a statistically significant interaction between post new baseline and visit. Similarly, as baseline varies between patients and there are limited patient numbers (n=20), the registry suggests extreme caution when interpreting results. The evidence suggests a positive impact on RULM scores in this population from baseline to 2.5 years (n=3). No non-EAP and EAP group sensitivity was conducted due to the groups not being considered comparable, as per the analysis for the RHS.

Types 2 and 3

An MMRM was conducted in type 2/3 patients for changes in RULM score. As with the previous analyses, weight was not a statistically significant predictor and was excluded from the model. There was a statistically significant interaction between visit and baseline RULM score, which was included in the model. There was evidence of an increase in RULM scores over time, from baseline to four years. At baseline, there were 58 patients and, at four years, six patients.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The adult registry reported a MMRM for RULM in type 2/3 non-sitters and sitters. For non-sitters, the mean change suggests improvement, however, there is minimal data. No statistical significance is observed; however, the numerical trend of improvement suggests potentially positive outcomes for these patients. The limited data suggests potential improvement but should be interpreted with caution due to lack of data, with data for 13 patients available at baseline and five at 2.5 years follow-up.

Similar results are observed for the walkers. No statistically significant changes occurred but the numerical trend suggests maintenance/small improvements in RULM scores over time. Again, data is limited at follow-up, with 34 patients at baseline and five patients at 4 year follow-up.

13.4.1.1.7 Motor Function Measure (MFM)

SLR evidence

There was no reported evidence for individual SMA types.

Multiple types

Two studies, reported in the earlier review,^{165,183} examined MFM in patients with either type 1 or type 2 SMA following nusinersen treatment. In one study, one subscale showed a non-statistically significant increase from 55% at baseline to 61% at follow-up.¹⁶⁵ The other study showed an increase in the median total score by 6 points.¹⁸³ These two studies reported the MFM32, while the updated review identified a further study using the MFM20 in an uncontrolled study. The mean change during nusinersen treatment, standardized over a 4-month period, was improved for both SMA1 (+4.1%, standardised response mean (SRM) 1.5) and SMA2 (+2.8%, SRM 0.89) patients.¹⁰⁵

13.4.1.1.8 Hammersmith Functional Motor Scale - Expanded (HFMSE)

SLR evidence

Presymptomatic

One study included in the previous review examined the impact of nusinersen on HFMSE in presymptomatic patients.³⁰ However, the original review did not report these results. For patients with 2 SMN2 and 3 SMN2 copies, continued improvement was observed.³⁰

New data from NURTURE provided detailed long-term HFMSE data for presymptomatic patients.^{175,176} At the first evaluable HFMSE assessment after two years of age, mean total scores were 34.5 for participants with two SMN2 copies and 46.4 for those with three SMN2 copies. At 48 months after this initial assessment, mean scores had increased to 52.3 in the 2-copy group (mean change from baseline of +18.7) and 64.9 in the 3-copy group (mean change of +20.0), out of a maximum possible score of 66. At the final study visit (Day 2891), the mean score was 56.1 (range: 30–66) for participants with two SMN2 copies and 65.9 (range: 65–66) for those with three SMN2 copies.^{175,176}

Type 1

Two studies, both reported in the earlier review,^{133,136} examined HFMSE in type 1 patients following nusinersen treatment. Both showed a significant increase in scores, one a mean increase from 14.7 to 18.8 at 48 months,¹³⁶ and the other an increase of 1.60 points compared to a mean decline in control group (-3.93 points) at 24 months.¹³³

Types 2 and 3

The previous review identified 17 records examining HFMSE in type 2/3 patients following treatment with nusinersen.^{28,113,124,133,141,168,177,206,213,214}

Four records reported data showing no change, or a stabilisation in scores of HFMSE following nusinersen,^{206,214-216} while one showed initial improvements which were not sustained at 12

months.¹⁵³ Improvements were observed from data in the remaining 11 records, with treated patients showing more improvements than control groups (CHERISH²⁸ and two other studies^{133,166}) and improvements reported following nusinersen treatment (eight studies, including CS2/12).^{124,164,168,177,204,205,213,217}

The current review identified six more studies examining HFMSE in type 2/3 patients.^{100,110,117,118,125,207} One of these studies included a control group.¹²⁵ (risk of bias could not be assessed for this study due to limited reporting of the methods). Two of the studies identified a statistically significant improvement in HFMSE score from baseline.^{100,207} Similarly, another study reported statistically significant increases in scores from baseline to 26 months.¹¹⁰ One retrospective controlled study observed increases in type 2 patients in HFMSE scores (+3.25 points per year) while the naïve control group decreased (-2.67 points per year). In type 3 patients both the treatment and naïve groups' scores increased, however, the increase in the treated group was numerically greater (+5.4 points per year vs +1 point per year, respectively).¹²⁵ Similarly, another retrospective cohort reported that type 2 patients showed a statistically significant increase from baseline to day 63 (12.5 vs 15, respectively). Type 3 patients' scores also increased over the same timeframe, but this was not statistically significant (44.2 to 47.2).¹¹⁷ Another study¹¹⁸ reported median (range) HFMSE scores and baseline and (median 134 month) follow-up of 4 (1-26) and 8 (4-30), respectively, for people with type 2 SMA. For people with type 3 SMA, the median (range) HFMSE scores were 41 (17-62) at baseline and 48 (28-64) at the (median 41 month) follow-up, respectively.

One study reported in the earlier review,¹⁴¹ examining type 2 patients only using nusinersen, reported a significant increase in mean HFMSE scores and a significant difference between the number of clinically meaningful increases in treated and untreated patients.¹⁴¹

The current review identified two further retrospective studies that were not previously reported, with both studies showing significant increases in HFMSE scores for type 2 patients.^{98,113}

One study reported in the earlier review,²⁰³ examined HFMSE in type 3 patients only following treatment with nusinersen. Treated patients showed statistically significantly improvements from baseline.²⁰³

Multiple types

The previous review identified 27 records reporting data assessing HFMSE in people with different SMA types following nusinersen. As reported in the earlier review, six studies showed stabilisation of scores amongst most or all of patients.^{178,186,188,189,208,209} One study showed both improvements and decline in HFMSE scores.¹⁹⁰ The remaining studies (including SHINE)¹²⁰ showed increases in HFMSE scores.^{120,167,169,172,173,182,184,185,191-196,199-201,210-212}

The updated review identified a further three uncontrolled studies examining HFMSE in people with different types of SMA type following nusinersen.^{101,106} A retrospective cohort reported on the clinical effectiveness of nusinersen, including clinically meaningful improvement, which was observed from two type 1 patients (100%), 11 type 2 patients (84.62%), and 2 type 3 patients (66.67%).¹⁰⁶ The other retrospective cohort reported statistically significant improvements from baseline to 14 months for patients on nusinersen treatment.¹⁰¹ Finally a prospective cohort observed similar findings, with improvements in scores for type 1, 2 and 3 patients (statistical significance is not reported).¹⁸²

13.4.1.1.9 Responder analysis

MAA evidence

Paediatric registry

The results for this outcome are taken from the updated April 2025 report.

The results of a responder analysis, defined as a 1 point increase in HINE score or 9 point increase in CHOP-INTEND score, was included. The results of this are reported in

Table . The registry provides some context on the results regarding the inclusion of those in the EAP. These patients were older and heavily symptomatic, while some were treated under compassionate use. Patients treated through the EAP were symptomatic at treatment initiation, however, they were younger and therefore less likely to have deteriorated as much as older patients, which means they may respond better to treatment. By the time the younger patients transitioned from the EAP to the MAA, they had already improved their CHOP-INTEND and HINE scores. This meant a higher baseline at MAA initiation. After an initial more rapid response, with increased scores of the motor scales, a plateau or slower response is common. A proportion of patients who had already achieved a relatively high baseline score at the time of starting nusinersen under the MAA, have been already treated with this drug for some time, but gains in scores have been missed. As expected, stabilisation is observed in these patients. The EAG would like to again highlight that a maintenance of motor function is equally important as gaining motor function, given the natural history and potentially rapid deterioration of motor functions that can be experienced.

Table 92: Responder analysis for nusinersen paediatric MAA patients

Nusinersen paediatric responders		Time point: patients achieved important improvement (n/N)							
Measure	Type	6 months	1 year	1.5 years	2 years	2.5 years	3 years	3.5 years	4 years
CHOP-INTEND	1 (EAP)	■	■	■	■	■	■	■	■
CHOP-INTEND	1 (Non-EAP)	■	■	■	■	■	■	■	■
CHOP-INTEND	2/3 non-sitters	■	■	■	■	■	■	■	■
CHOP-INTEND	2/3 sitters	■	■	■	■	■	■	■	■
CHOP-INTEND	2/3 walkers	■	■	■	■	■	■	■	■
HINE-2	1 (EAP)	■	■	■	■	■	■	■	■
HINE-2	1 (Non-EAP)	■	■	■	■	■	■	■	■
HINE-2	2/3 non-sitters	■	■	■	■	■	■	■	■
HINE-2	2/3 sitters	■	■	■	■	■	■	■	■
HINE-2	2/3 walkers	■	■	■	■	■	■	■	■

Abbreviations: CHOP INTEND = Children's Hospital Of Philadelphia Infant Test Of Neuromuscular Disorders; N = number of patients with evaluable data; n = number of patients who achieved important improvement; EAP = Expanded Access Programme; HINE-2 = Hammersmith Infant Neurological Examination 2

Adult registry

The adult registry report did not include a responder analysis. The CHOP-INTEND and HINE-2 outcomes used in the responder analysis are not applicable to adults, as previously stated.

13.4.1.1.10 ATEND

SLR evidence

No evidence from the original or updated review was identified for this outcome.

MAA evidence

Paediatric registry

The paediatric registry did not report on this outcome. The intended age range for this tool is still to be confirmed.¹⁹⁸

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The adult registry reported a MMRM for ATEND left and right in type 2/3 non-sitters and sitters. For non-sitters, the mean change suggests improvement. There is minimal data with short follow-up (12 months) due to number of patients available. No statistical significance is observed. However, the numerical trend of improvement suggests potentially positive outcomes for these patients. The limited data suggests potential improvement but should be interpreted with caution due to lack of data, with data for five patients available at baseline and four at 12 months.

The ATEND was utilised in less functional sitters (RHS <6); these individuals show an unusual degree of symptomatic progressions. Baseline included 12 patients, with follow-up to 2.5 years showing varying mean scores. The results show no statistically significant reductions or improvement and numerical trends are less obvious than for the non-sitter patients. The limited data means the results should be interpreted with caution.

13.4.1.1.11 Sitting position

SLR evidence

Type 1

The review update identified a single, uncontrolled study that examined sitting position in type 1 patients when treated with nusinersen.¹⁰³ This study was part of the EAP and reported that 5 of 30 patients acquired a stable, support-free sitting position (> 30 seconds).¹⁰³

There was no reported evidence for any other SMA types.

13.4.1.1.12 Compound Motor Action Potential (CMAP)

SLR evidence

Presymptomatic

The original review identified a record reporting data from the NURTURE trial, examining the effectiveness of nusinersen on CMAP; scores remained stable.³⁰ They also reported

information from a previous European Medicines Agency assessment report (study: SM201). However, this data is from the NURTURE trial and is therefore not reported separately.¹⁷⁴

New data provided long-term CMAP findings from the NURTURE study, including assessments of both ulnar and peroneal nerves in presymptomatic patients treated with nusinersen.^{175,176}

Ulnar nerve

At baseline, the mean (SD [range]) ulnar nerve CMAP amplitude was 2.69 (1.516 [1.0–6.7]) mV in participants with two SMN2 copies (n=14) and 3.11 (1.119 [1.8–4.9]) mV in those with three SMN2 copies (n=10). At Day 2891, mean amplitudes had increased to 7.23 (4.466 [2.3–16.7]) mV for the two-copy group (n=8) and 9.01 (3.658 [4.2–16.0]) mV for the three-copy group (n=8). Improvements in ulnar CMAP amplitudes were consistently greater in participants with three SMN2 copies throughout the study.^{175,176}

Peroneal nerve

Baseline mean (SD [range]) peroneal nerve CMAP amplitude was 3.52 (2.159 [1.1–9.7]) mV in participants with two SMN2 copies (n=12) and 3.75 (2.188 [0.2–7.0]) mV in those with three SMN2 copies (n=10). While peroneal CMAP amplitudes fluctuated over time, the mean values did not decrease relative to baseline. Up to Day 1611, mean amplitudes were similar between the two groups. After Day 1611, values stabilized in participants with three SMN2 copies but continued to increase in the two-copy group.^{175,176}

Type 1

One record in the original review reported data examining CMAP in type 1 patients following nusinersen; 36% of the treatment group were classified as responders compared to 5% of the control group (ENDEAR).²⁷

Types 2 and 3

The original review identified two records that reported data examining CMAP in type 2/3 patients following nusinersen.^{124,204} One reported an increase of 0.4 mV in type 2 patients and 0.3 mV in type 3 patients (CS2/12),²⁰⁴ whilst the other showed no significant changes after nusinersen treatment.¹²⁴ The original review also identified one study examining CMAP in type 3 only patients following nusinersen and found no significant differences between SMA patients and healthy individuals.¹⁴⁵

The current review identified two further studies assessing CMAP in type 2/3 patients treated with nusinersen.^{122,207} One of these was a controlled prospective study (ROBINS-I rating: serious) that reported no statistically significant differences between groups at 12 months for median and ulnar nerve.¹²² The other, uncontrolled, prospective study reported a CMAP value of the trapezius muscle ≥ 1.76 mV, suggesting that patients were more likely to respond to treatment by day 300 (sensitivity 84.6%, specificity 85.7%).²⁰⁷

Multiple types

The original review identified three studies that assessed CMAP in patients with different types of SMA following nusinersen treatment. Increases were seen across all three.^{163,188,189} Scores were higher in patients with 4 SMN2 copies compared to 2 or 3 SMN2 copies.¹⁶³ The largest improvements in CMAP values were recorded in SMA type 1 patients, which were statistically correlated with scores on CHOP scales ($p < 0.001$).¹⁸⁸

Unreported type

The original review identified three studies that assessed CMAP in patients with an unreported SMA type following nusinersen treatment. All studies reported some increase in CMAP,^{131,197,218} with scores plateauing after day 568 in one study,¹³¹ and increases in symptomatic patients not reaching levels of asymptomatic patients in another.¹⁹⁷

13.4.1.1.13 Motor Unit Index (MUNIX)**SLR evidence**

There was no reported evidence for presymptomatic or type 1 SMA.

Types 2 and 3

The current review identified one study which examined MUNIX in type 2/3 patients receiving nusinersen. This prospective, uncontrolled, study reported that upper limb improvements were superior to lower limb improvements. As this is a conference abstract, no further details are provided.²⁰⁷

13.4.1.1.14 Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R)**SLR evidence**

There was no reported evidence for presymptomatic or type 1 SMA.

Types 2 and 3

In the original review, three studies reported on ALSFRS-R in type 2/3 patients following nusinersen. All three reported an increase of one point.^{202,206,217} In one of these, the increase was observed in type 3 patients only,²¹⁷ and in one the increase was observed in type 2 patients only.²⁰²

Multiple types

In the original review two studies examined ALSFRS-R in mixed SMA types following nusinersen. One reported a 67.3% improvement in scores, with 32.7% remaining unchanged.²⁰¹ The other observed that treated patients experienced clinically meaningful improvements.¹⁶⁹

13.4.1.1.15 Medical Research Council Sum Score (MRC-SS)**SLR evidence**

There was no reported evidence for presymptomatic or type 1 SMA.

Types 2 and 3

The original review identified two studies examining MRC-SS in type 2/3 patients following nusinersen.^{213,217} Increases were seen in type 3 patients only in one study,²¹⁷ with an average change of 3.9 points at 24 months in treated patients²¹⁵ and significant increases in ambulatory patients only.²¹³

Multiple types

The original review identified one study examining MRC-SS in people with different SMA types following nusinersen. MRC sum scores improved on average 2.4–2.5 points at months 6–14, respectively.²⁰⁸

13.4.1.1.16 *Manual Muscle Testing (MMT)*

SLR evidence

There was no reported evidence for presymptomatic or type 1 SMA.

Types 2 and 3

The original review identified one study which included 37 patients examined using MMT of type 2/3 SMA type following nusinersen treatment. The scores increased at six months and 14 months.²⁰²

13.4.1.1.17 *Motor Unit Number Estimation (MUNE)*

SLR evidence

There was no reported evidence for presymptomatic or type 1 SMA.

Types 2 and 3

The original review identified two records that reported data for the assessment of MUNE in type 2/3 patients treated with nusinersen.¹⁴⁵ One of these records, which reported data from the CS2/12 trial, examined MUNE in type 2 and 3 following nusinersen and showed an increase for type 2 patients by 2.0 points, and a decrease for type 3 patients by 29.6 points.²⁰⁴ One study examined MUNE in type 3 patients only following nusinersen and showed no significant differences overall.¹⁴⁵

Multiple types

The original review identified one study examining MUNE scores in people with different types of SMA following nusinersen, and showed increased scores.¹⁸⁹

13.4.1.1.18 *Grip and Finger Flexion Strength (GFFS)*

SLR evidence

There was no reported evidence for presymptomatic or type 1 SMA.

Types 2 and 3

The original review identified two studies reporting GFFS in type 2/3 patients following nusinersen.^{215,216} GFFS increased in all cohorts at follow-up²¹⁶ and three patients reported increased hand strength.²¹⁵

Multiple types

The original review identified one study examining GFFS in a range of SMA types following nusinersen and showed a significant increase in scores, and a significantly higher dominant hand score.²⁰⁸

13.4.1.1.19 *6 minute walk test*

SLR evidence

Presymptomatic

One study included in the original review examined the impact of nusinersen on the 6MWT in pre-symptomatic patients,³⁰ however, the original review did not report these results. In 11 presymptomatic children (two SMN2 copies = 5; three SMN2 copies = 6) there was evidence of sustained independent walking (ranges: 150-325 metres and 238-444 metres, respectively).³⁰

New final analysis data from NURTURE (2024) provided further detail on 6MWT outcomes in presymptomatic patients treated with nusinersen in study 232SM201. Participants who achieved independent ambulation were able to perform the 6MWT at various time points throughout the study (up to Day ~2892), with distances ranging from 50 to 594 metres. Mean walking distances generally increased over time, and overall, distances were consistently higher in participants with three SMN2 copies compared to those with two. These findings support the durability of ambulatory function in this cohort following early treatment.^{175,176}

Type 1

The original review included one study examining the effectiveness of nusinersen in the 6MWT. One participant improved and was able to walk 165 metres at 48 months.¹³⁶

Types 2 and 3

The original review included four records that reported 6MWT assessments in type 2/3 patients following nusinersen.^{203,204,217}

In one study, it was reported that 78% of patients showed a clinically meaningful improvement.²¹⁷ Another record, which reported data from the CS2/12 trial, reported that 100% patients achieved a clinically meaningful improvement by day 1050, but 1/11 type 2 patients gained the ability to walk independently, and in type 3, 2/4 lost the ability to walk at baseline and regained it during treatment.²⁰⁴ Distance walked in the 6MWT increased significantly, with the rate of patients achieving a clinically meaningful improvement increasing from 53% to 69% of patients.²⁰⁵

The updated review identified two further, uncontrolled studies assessing type 2/3 patients.^{119,207} Both studies were prospective cohorts. One showed a non-statistically significant improvement in 6MWT from baseline to 14 months (11.9 metres, n = 11).¹¹⁹ The other reported improvements in 6MWT at visits, however, the timeframe is not explicitly stated: at visit four, 5/15 improved; at visit five, 9/15 improved; and at visit six 12/15 improved.²⁰⁷

One study reported in the original review assessed 6MWT in type 3 patients only following nusinersen, showing no significant increase in scores.²⁰³ The updated review identified one prospective cohort study reporting 6MWT in type 3 patients only following nusinersen, in which five patients increased the average distance from baseline (100.9 metres) to follow-up (158 metres).¹⁸² The updated review also identified a retrospective cohort study reporting the impact of nusinersen on the 6MWT in type 3 patients.¹¹⁷ The results suggested no statistically significant improvements between baseline and 63 days follow-up (199.9 vs 226.3 metres, respectively).¹¹⁷

Multiple types

The original review identified 12 studies examining 6MWT in mixed SMA types following nusinersen treatment.^{169,182,190,192,195,200,201,208,209,211,212} The majority of these studies showed

improvement. Studies reported no significant increase in ambulatory patients,²⁰⁸ no significant increase in four patients,¹⁹² a worsening in 33% patients (along with a clinically meaningful increase of 50%).¹⁸⁵ One study showed an increase in distance amongst later-onset patients.²⁰¹ The remaining studies reported increases in 27.2% paediatric patients and 26.5% adult walkers,²⁰⁹ and overall improvements or clinically meaningful increases.^{169,182,190,195,200,211,212}

The updated review identified two further, uncontrolled studies assessing the 6MWT in a group of people with mixed SMA types following nusinersen treatment.^{101,219} One of these was a conference abstract for the SHINE study, which reported that three patients (of five) improved their 6MWT (range of improvement: 24 to 81 metres).²¹⁹ The other study was a retrospective cohort which showed stabilisation of the 6MWT from baseline to 14 months (339.2 to 343.3 metres, respectively).¹⁰¹

Unreported type

The original review identified two studies that examined 6MWT in unreported SMA type following nusinersen.^{146,218} One study showed a variable increase in distance walked,²¹⁸ whilst the other reported that SMA patients achieved half the distance walked by control patients.¹⁴⁶

MAA evidence

Paediatric registry

The paediatric registry did not report on this outcome. However, the 10 metre run test was conducted as part of the RHS, results of which can be seen in section 13.4.1.1.5.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The adult registry conducted MMRM in type 2/3 walkers for the 6 minute walk test (6MWT). No statistically significant changes are reported. The data trends towards maintenance and the registry suggest that this test captures performance fatigability, which is not captured in other functional groups. Stabilisation of a 6MWT is a good outcome as it could represent no changes in muscular fatigue. Data availability is low, with 21 patients with data available at baseline and five patients with data at 4 years follow-up.

13.4.1.1.20 Timed Up and Go (TUG)

SLR evidence

There was no reported evidence by individual SMA type.

Multiple types

The original review identified one study examining TUG in people with a range of SMA types following nusinersen and showed that scores became faster over time.²²⁰

Unreported type

The original review identified one study reporting TUG following nusinersen where SMA type was unreported. SMA patients completed TUG in 21.3 seconds compared to control patients completing in 4.3 seconds.¹⁴⁶

13.4.1.1.21 Unspecified motor function assessments

SLR evidence

There was no reported evidence by individual SMA type.

Multiple types

The current review identified five uncontrolled studies that considered unspecified tools for motor function assessments for patients with different types of SMA receiving nusinersen (i.e. tools that were not explicitly named).^{102,106,182,221,222}

Motor function status (non-sitter, supported sitter, independent sitter, supported walker, and independent walker) was considered by one prospective, non-comparative, study.¹⁸² The results were reported as number of patients in each category at baseline and follow-up (with the time-point unclear, at either 6 or 12 months). It stated that type 1 patients were all non-sitters at baseline (n = 8), while at follow-up three remained non-sitters, three became supported sitters, and two became independent sitters. For type 2 patients, at baseline all were independent sitters (n = 7), five remained independent sitters, one became a supported sitter, and one became a supported walker. Finally, at baseline one type 3 patient was a supported walker and seven were independent walkers. At follow-up, one remained a supported walker and another became a supported walker, with the remaining six patients maintaining independent walker status (see Table 93).

Table 93: Overview of the results from Ip and colleagues 2024¹⁸² of changes in motor functions status

Motor Function Status	Baseline n	Follow-up n
Non-sitter	- Type 1: 8 - Type 2: 0 - Type 3: 0	- Type 1: 3 - Type 2: 0 - Type 3: 0
Supported Sitter	- Type 1: 0 - Type 2: 0 - Type 3: 0	- Type 1: 3 - Type 2: 1 - Type 3: 0
Independent sitter	- Type 1: 0 - Type 2: 7 - Type 3: 0	- Type 1: 2 - Type 2: 5 - Type 3: 0
Supported Walker	- Type 1: 0 - Type 2: 0 - Type 3: 1	- Type 1: 0 - Type 2: 1 - Type 3: 2
Independent Walker	- Type 1: 0 - Type 2: 0 - Type 3: 7	- Type 1: 0 - Type 2: 0 - Type 3: 6
Abbreviations: n = number of patients		

Another prospective, non-comparative, study reported that 66% of patients improved in muscle strength or in QoL. Additionally, there was evidence of stabilisation of respiratory and swallowing function. Information was from a conference abstract and no further details are provided, which makes interpretation of the results difficult.¹⁰² A further comparative

prospective study only provided baseline data (number of non-sitters, sitters, and walkers) and no follow-up information, therefore, no results from this study can be included.²²¹

A retrospective cohort identified motor milestone response. For type 1, four participants (33.3%) responded, in type 2 13 participants (50%) responded, and three type 3 participants (75%) responded. This equates to 20 patients responding to treatment in terms of motor milestones overall (74.1%). However, this result was not statistically significant.¹⁰⁶ Finally, a retrospective comparative chart review reported that improvement or maintenance in motor milestones was achieved by 5 of 10 patients receiving nusinersen monotherapy (mean time to initial improvement in any motor milestone: 7.3, standard error = 3.8 months).¹⁵⁸

13.4.1.2 Bulbar function

SLR evidence

13.4.1.2.1 Nutritional support including nasogastric feeding and gastrostomy

Presymptomatic

One study from the earlier review,³⁰ examining the effect of nusinersen on the bulbar function in those with presymptomatic SMA, reported that the majority of participants maintained their ability to swallow, as most never gagged or choked on liquid or solids. In addition, participants' parents were also reportedly not concerned about choking or aspiration during meals.

New final analysis data from NURTURE (2024) further evaluated bulbar function in presymptomatic patients treated with nusinersen in study 232SM201, using both HINE-1 and the Paediatric Functional Oral Intake and Swallowing Assessment (PASA).^{175,176} Based on HINE-1 (suck/swallow) assessments up to Day 778, 12 of 15 participants with two SMN2 copies maintained normal suck/swallow function from baseline to the last assessment. None of the participants with three SMN2 copies experienced a decline in suck/swallow function. Dysphagia symptoms were infrequent and generally mild throughout the study.^{175,176}

According to PASA outcomes up to Day 2891, five of the 15 participants with two SMN2 copies demonstrated consistent bulbar disability. The remaining 10 participants in this group retained more consistent normal function and did not require gastric tube support. All 10 participants with three SMN2 copies showed predominantly normal bulbar function.^{175,176}

Type 1

Seven studies^{73,130,132,133,135,136} in the earlier review examined the effects of nusinersen on bulbar function in type 1 SMA. As reported in the review, one study¹³⁶ showed some improvement in feeding following nusinersen treatment. Two studies showed either no change¹³⁰ or stability,¹³³ while three studies^{73,132,135} showed a decline in the ability to feed orally following treatment.

One new study was identified in this review update¹¹⁵ which reported that the numbers and rates of gastrostomy-fed patients were 18 (64%) in the nusinersen group and 2 (6%) in the treatment-naïve (control) group. Furthermore, the numbers (%) who were nasogastric tube fed were 4 (14%) and 31 (86%) in the treatment and control groups, respectively. Finally, two (7%) of the nusinersen-treated patients were nasogastric tube fed (NGT) with some oral intake (n/% NR for the control group). Another newly identified study¹¹⁸ reported that two patients required feeding with percutaneous gastrostomy and one with a nasogastric tube.

Types 2 and 3

Two studies^{162,177} from the earlier review reported bulbar function in type 2 and 3 SMA patients. Mastication and swallowing was reported to be stable among those treated after 16 months in one study.¹⁶² In another study,¹⁷⁷ an increased need for tube feeding was reported following nusinersen treatment.

Multiple types

Nine studies^{104,121,158,180,183,184,190,192,223} reported on the impact of nusinersen treatment on bulbar function in relation to nutritional support in individuals with mixed types of SMA. In the original review, four studies^{121,184,190,192} indicated a general decline in bulbar function following nusinersen treatment, particularly in relation to feeding, with these studies noting an increased number of patients requiring tube feeding or additional support. Additionally, one study¹⁸³ specifically reported a non-significant increase in the number of patients needing feeding support after nusinersen treatment in SMA types 1 and 2.

Four newly identified studies^{104,180,223} provided further insights into nutritional support among patients with mixed types of SMA. In one study,²²³ investigators observed that while most patients showed no change, some experienced notable improvements in swallowing or feeding ability following nusinersen treatment.

In another study,¹⁰⁴ the need for gastrostomy was reported in relation to treatment adherence among patients with different types of SMA. The need for gastrostomy was higher in non-adherent participants compared to adherent ones (SMA type 1 58.3% for non-adherent vs. 36.4% for adherent; SMA type 2 44.8% for non-adherent vs. 0% for adherent; SMA type 3 21.4% for non-adherent vs. 18% for adherent). The highest need was observed in non-adherent SMA type 1 patients (n=12), with seven (58.3%) requiring gastrostomy, followed by non-adherent SMA type 2 patients (n=29), with 13 (44.8%) requiring gastrostomy. No gastrostomy was reported among adherent SMA type 2 patients (n=12). Similarly, another newly identified study,¹⁸⁰ reporting on the impact of nusinersen on the need for gastrostomy support, showed increased need for gastrostomy from four participants at baseline to 14 after three years.

Also, as reported by another newly identified study,¹⁰⁴ the need for nasogastric or other non-oral feeding support assessed between adherent and non-adherent groups showed a higher need among non-adherent participants (SMA Type 1 33.3% for non-adherent vs. 27.3% for adherent; SMA type 2 37.9% for non-adherent vs. 0% for adherent; SMA type 3 21.7% for non-adherent vs. 18% for adherent). The highest need was among non-adherent SMA type 2 patients (n=29), with 11 (37.9%) requiring support, followed by non-adherent SMA type 1 patients (n=12), with 4 (33.3%). No nasogastric tube feeding was reported among adherent SMA type 2 patients (n=12). Like the adherent SMA type 2 results, no patients needed nasogastric feeding support another newly identified study¹⁸⁰ following three years of nusinersen treatment.

Finally, another newly identified study¹⁵⁸ reporting real-world outcomes in patients with multiple types SMA treated with either nusinersen monotherapy or OA monotherapy found that half of the patients receiving nusinersen experienced either improvement or maintenance in eating function. This outcome was more pronounced in those receiving OA, with 5 out of 6 showing positive results.

Unreported type

Two studies examined feeding in patients with unreported SMA type receiving nusinersen. The need for a feeding tube increased during treatment in one study,¹³⁷ while another study¹²⁷ showed a decline in feeding score.

13.4.1.2.2 Swallowing function

Type 1

One study¹³⁰ in the original review observed a reduced deterioration in swallowing following nusinersen treatment in type 1 SMA participants, while in another study⁷³ from the existing review, a decline in swallowing function was observed.

Types 2 and 3

One study²¹⁴ included in the earlier review showed a preservation of swallowing function without further significant decline in bulbar function in participants with type 2/3 SMA.

13.4.1.2.3 Speech therapy support

Multiple types

Two newly identified studies^{102,158} reported on the need to receive speech therapy support in the participants with different types of SMA receiving nusinersen. In one newly identified study¹⁰⁴ the distribution of the speech therapy support received was assessed between those who were adherent and non-adherent to nusinersen therapy. The study showed that higher number of non-adherent participants received speech therapy support than the adherent participants (SMA Type 1 50% for non-adherent vs. 9.1% for adherent; SMA Type 2 34.5% for non-adherent vs. 0% for adherent; SMA Type 3: 9.0 % for non-adherent vs. 8% for adherent). The highest need was among non-adherent SMA type 1 participants (n=12), with half (50%) requiring some form of speech therapy support. No speech therapy was reportedly needed among adherent SMA type 2 patients (n=12).

13.4.1.2.4 Miscellaneous

Presymptomatic

One new study,¹¹⁴ reporting on presymptomatic patients who received early treatment which achieved timely acquired World Health Organization motor development milestones and did not experience feeding problems.

Multiple types

One newly identified study¹⁵⁸ reporting real-world outcomes in patients with multiple types SMA treated with either nusinersen monotherapy or OA monotherapy found that half of the patients receiving nusinersen experienced either improvement or maintenance in cry function. This outcome was more pronounced in those receiving OA treatment, with all of them showing positive results. The same newly identified study¹⁵⁸ found that 7 of 8 participants receiving nusinersen experienced either improvement or maintenance in speech function while all those receiving OA treatment showed either improvement or maintenance in speech function.

Another new study⁹⁹ reported that, amongst 7/37 nusinersen-treated patients for whom 10-month follow-up data were available, there were no significant changes in the decline of three measures of facial nerve vulnerability, namely the CMAP amplitude (from 2.13 ± 0.97 to 1.49 ± 0.97 , $P=0.1094$), the MUNIX of orbicularis oculi (from 31.31 ± 14.52 to 29.51 ± 23.42 , $P=0.5781$), and the MUSIX (from $66.68 \mu V \pm 18.23$ to $49.27 \mu V \pm 8.98$, $P=0.0625$).

13.4.1.3 Hospitalisation

SLR evidence

Presymptomatic

New final analysis data from NURTURE by Tichler et al. (2024) provide long-term hospitalisation outcomes for presymptomatic patients treated with nusinersen in study 232SM201. Hospitalisations were infrequent and primarily related to acute, self-limiting respiratory infections. No long-term hospitalisation or intensive care unit (ICU) admission was required. Additionally, among participants with two SMN2 copies, the rate of hospitalisation due to respiratory events decreased over time.^{175,176}

Type 1

New data extracted from a conference abstract by Arjunji et al. (2019) compared patients treated with OA (CL-101 study) to those treated with nusinersen (ENDEAR study), using a retrospective model of projected healthcare resource utilisation²²⁴. The reported unadjusted annualised rate of hospitalisations was 4.5 per patient-year for nusinersen-treated patients (up to 13 months follow-up), compared with 2.1 per patient-year for OA-treated patients (up to 24 months follow-up). The mean proportion of time spent hospitalised was also higher in the nusinersen group (11.4%; range 0–50%) compared to the OA group (4.4%; range 0–18.3%). Additionally, 18% of nusinersen-treated patients spent $\geq 20\%$ of their follow-up period in hospital, whereas no patients in the OA group reached this threshold.²²⁴

Types 2 and 3

Hospitalisation outcomes for later-onset SMA were primarily informed by the CHERISH trial, which assessed nusinersen in children with SMA Types 2 and 3. Although hospitalisation was not a prespecified endpoint, serious adverse events (SAEs), many of which necessitate inpatient care, were used as a proxy measure.¹ As reported by Mercuri et al (2018) and cited in the EMA assessment (2023), SAEs occurred in 17% of nusinersen-treated participants, compared with 29% in the control group over the 15-month treatment period.²⁸ Moreover, no SAEs were considered by the Investigator to be related or possibly related to the study treatment.⁶⁸

13.4.1.4 Respiratory function

13.4.1.4.1 FVC

SLR evidence

Presymptomatic

New final analysis data from NURTURE (2024) provide long-term respiratory function outcomes for presymptomatic patients treated with nusinersen in study 232SM201. Overall, respiratory parameters improved across participants. The average phase angle—a surrogate measure of thoracoabdominal synchrony—remained within normal ranges for both SMN2 groups (2-copy group: 16.56 to 24.40 degrees; 3-copy group: 13.27 to 18.54 degrees). Most participants remained off respiratory support throughout the study.^{175,176} Five of 15 participants (33%) with two SMN2 copies met the predefined primary endpoint, which was defined as receiving invasive or non-invasive ventilation for ≥ 6 hours/day continuously for ≥ 7 days, or requiring tracheostomy. Notably, none of the 10 participants with three SMN2 copies met this endpoint. Importantly, no participants died or required a tracheostomy. Among the five participants who met the ventilation endpoint, four events were associated with acute,

reversible infections. All five participants continued to gain motor milestones. None of the participants required permanent ventilation, defined as ≥ 16 hours/day continuously for >21 days in the absence of an acute reversible event or tracheostomy.^{175,176}

Types 2 and 3

Three studies,^{112,119,225} two newly identified and one from an earlier review, examined the impact of nusinersen treatment on forced vital capacity (FVC) in individuals with type 2 or 3 SMA. The study included in the earlier review reported no significant change in FVC after treatment.²²⁵

One of the new studies¹¹² reported a slower annual decline in FVC among treated participants compared to the expected natural progression of the disease. Specifically, the decline was 2.2% per year versus 4.2% in type 2 SMA, and 1.4% versus 6.3% in type 3 SMA. In the other new study,¹¹⁹ FVC remained stable following nusinersen treatment, with no significant change in the percent predicted FVC (mean change 0.1 ± 8.6 , $P>0.05$).

Multiple types

Ten studies, eight from the previous review and two newly identified records, examined the effects of nusinersen on respiratory function in individuals with different types of SMA. Among the studies included in the earlier review, four reported improvements in FVC and overall respiratory function,^{169,178,208,220} while three found no significant change in FVC following treatment.^{193,209,226} One study¹⁹² noted a decline in respiratory function in a single patient after treatment.

Of the two new studies, one study¹¹⁶ found that overall FVC remained stable over a 22-month follow-up period (mean monthly change -0.047 , 95% CI -0.115 to 0.020 ; $P=0.17$), though outcomes varied by SMA type. Patients with type 2 SMA showed a significant increase in FVC ($+0.144$, 95% CI 0.086 to 0.202 ; $P<0.0001$), while those with type 3 or type 4 SMA experienced a significant decrease (-0.142 , 95% CI -0.239 to -0.044 ; $P=0.005$). The second new study²²⁷ evaluated a paediatric cohort with different types of SMA and found no significant improvement in mean FVC over approximately 13 months of nusinersen treatment ($+0.4$; $P=0.90$).

One study¹⁶⁵ included in the earlier review examining respiratory function in patients with type 1 and 2 following treatment with nusinersen, reported better respiratory muscle strength and significantly better forced vital capacity (FVC) in patients with type 2 SMA compared to control.

13.4.1.4.2 PFVC

SLR evidence

No evidence was reported for presymptomatic or type 1 patients.

Types 2 and 3

One new study¹¹⁹ examining the impact of nusinersen treatment in type 2 and 3 SMA patients reported stability but no significant mean change in the % of predicted FVC (0.1 ± 8.6 , $P>0.05$).

13.4.1.4.3 FEV1

SLR evidence

No evidence was reported for SMA types separately.

Multiple types

One new study²²⁷ examined the impact of nusinersen treatment in patients with different types of SMA on FEV1, and showed a significant increase in the mean values of FEV1 (+4.4; P=0.03) in all patients at approximately 13 months following nusinersen treatment.

*13.4.1.4.4 Maximum inspiratory pressure**SLR evidence*

No evidence was reported for presymptomatic or type 1 patients.

Types 2 and 3

One newly identified study¹¹⁹ assessed the impact of nusinersen on maximum inspiratory pressure (MIP) in patients with type 2 and 3 SMA. The study reported stable respiratory performance with no significant mean change in MIP from baseline through to month 14 ($-0.6 \text{ cm H}_2\text{O} \pm 16.4$; $P>0.05$).

*13.4.1.4.5 Maximum expiratory pressure**SLR evidence*

No evidence was reported for presymptomatic or type 1 patients.

Types 2 and 3

One newly identified study¹¹⁹ examined the impact of nusinersen treatment on maximum expiratory pressure in type 2/3 SMA patients. The study reported stable respiratory function with no significant mean change in the maximum expiratory pressure from baseline through to month 14 ($11.1 \text{ cm H}_2\text{O} \pm 41.2$; $P>0.05$).

Multiple types

One newly identified study¹¹¹ investigating the effect of nusinersen treatment in different types of SMA showed that a significant improvement in maximum expiratory pressure was observed in participants over 18 months, with a significant increase of $12.74 \text{ cm H}_2\text{O}$ ($t(32) = -3.18$; $P=0.003$).

*13.4.1.4.6 Sniff nasal inspiratory pressure**SLR evidence*

No evidence was reported by individual SMA type.

Multiple types

One newly identified study¹¹¹ investigating the effect of nusinersen treatment in SMA types SMA 2, 3 and 4 showed a significant improvement in sniff nasal inspiratory pressure in participants aged over 18 months, with a significant mean increases of $11.82 \text{ cm H}_2\text{O}$ ($t(32) = -4.14$, $P<0.001$).

13.4.1.4.7 Peak expiratory flow (PEF)

No evidence was reported by individual SMA type.

Multiple types

Two newly identified studies^{111,227} examined the impact of nusinersen treatment on PEF in individuals with different types of SMA. One study¹¹¹ reported a non-significant improvement in PEF among participants over an 18 month period ($t(32) = 1.87$, $P=0.071$). In the second study, the overall mean PEF percentage remained stable and showed no further decline in patients with mixed SMA type. However, a significant increase in average PEF was observed in the type 2 SMA subgroup (2.9%, $p = 0.03$).²²⁷

13.4.1.4.8 Miscellaneous

Type 1

Three studies from the original review^{128,132,133} investigated the effectiveness of nusinersen on other markers of respiratory function in patients with type 1 SMA. One study¹²⁸ reported improvements in respiratory function in most patients. Another study¹³² found that all patients required respiratory support, and a third study¹³³ observed a reduction in the duration of ventilatory support in most patients.

Types 2 and 3

Two studies^{202,205} included in the earlier review reported that no improvement was seen in other measures of respiratory function.

Multiple types

One study¹⁰² with an updated result from the earlier review showed that an improvement in muscle strength or quality of life and stabilisation of respiratory function were seen in 66% of patients.

13.4.1.4.9 Tracheostomy

SLR evidence

No evidence was identified for this outcome in the review process.

MAA evidence

Paediatric registry

The results for this outcome are taken from the updated April 2025 report.

The registry stated that only two type 1 EAP patients had tracheostomies.

Adult registry

This outcome was not reported in the adult registry report.

13.4.1.5 Complications of SMA

Presymptomatic

New final analysis data from NURTURE (2024) provide long-term safety data on complications in presymptomatic patients with genetically confirmed 5q SMA treated with nusinersen. Over the five-year follow-up period, there was a low incidence of failure to thrive, dysphagia, and orthopaedic complications. Growth parameters either remained stable or showed improvement throughout the study, supporting a favourable long-term safety and developmental profile in this population.^{175,176}

Types 2 and 3

All data in this section are drawn from previously published sources and were also referenced in the Warwick EAG report. According to the previous MTA report, complications in patients with later-onset SMA (Types 2 and 3) were most prominently reported in studies related to the CHERISH (NCT02292537) and SHINE (NCT02594124) trials.¹ Mercuri et al (2018), based on the CHERISH trial, reported the occurrence of respiratory complications including pneumonia and respiratory distress. These complications were observed in both nusinersen and control groups, suggesting they may reflect the natural course of the disease rather than being treatment-related adverse effects. Importantly, the overall safety profile remained favourable throughout the study period.²⁸

As noted in the previous MTA report, further longitudinal insights were provided by Dunaway Young et al (2023), based on results from the SHINE extension study, which explored scoliosis progression in participants treated with nusinersen. An analysis of changes in Cobb angle revealed progressive scoliosis in a proportion of participants, which was associated with lower improvements in motor function as measured by HFMSE and RULM scores. Although not a direct adverse event of the treatment, scoliosis progression remains a known complication of SMA that may influence the functional outcomes of therapeutic interventions.^{1,120}

Multiple types

One newly-identified study by Masson et al reported that three patients with type 1, 14 with type 2 and three with type 3 developed scoliosis before treatment. During treatment, eight patients with type 1 SMA and three patients with type 3 SMA developed scoliosis. Scoliosis surgery was performed for two patients with type 2 SMA.¹⁰⁷

13.4.1.6 Need for non-invasive or invasive ventilation

SLR evidence

Presymptomatic

New final analysis data from NURTURE (2024) assessed the need for ventilatory support among presymptomatic patients with 5q SMA treated with nusinersen. Over the course of the study (up to Day 2892), 5 out of 15 participants with two SMN2 copies met the composite primary endpoint of death or need for ≥ 6 hours/day of respiratory support for at least seven consecutive days, or tracheostomy. No participants with three SMN2 copies met this endpoint. Importantly, no deaths or tracheostomies occurred in either group. Among the five participants who required non-invasive ventilation, four events were related to acute, reversible infections. One participant required ≥ 16 hours/day of ventilation for over 21 days but subsequently recovered, and did not progress to permanent ventilation. At the final study visit (Days 2878–2917), all five participants remained on non-invasive ventilation (6–10 hours/day), but none required permanent ventilation.^{175,176}

Furthermore, recent long-term follow-up data from Crawford et al. (2023) reported that, over five years of treatment, none of the children with type 1 or 2 SMA required permanent ventilation.³⁰

Type 1

As noted in the previous MTA report, data from Finkel et al. (2021) reported results from the ENDEAR trial (NCT02193074), which evaluated nusinersen in infants with symptomatic type 1 SMA.¹ Participants in the nusinersen group had a 47% lower risk of requiring permanent

ventilation or death compared to the control group (HR 0.53, 95% CI 0.32–0.89; P=0.005).¹³¹ Although the overall rate of permanent assisted ventilation use was lower in the nusinersen group, the result did not reach statistical significance (HR, 0.66; P=0.13). Long-term follow-up data from the SHINE extension supported this trend, with lower-than-expected rates of ventilatory support reported over time.¹³¹

New data from an additional evaluation by Arjunji et al (2019), comparing OA and nusinersen, showed that no participants required permanent ventilation in the OA group during a follow-up of more than 24 months. Ventilation outcomes were also favourable among nusinersen-treated participants, although specific comparative figures were not fully detailed.²²⁴

Another newly identified study¹¹⁵ reported that the number (%) of patients who received NIV was 26 (93%) in the nusinersen group and 15 (41%) in the treatment-naïve control group. The same study reported that cough assist was administered to 25 (96%) in the nusinersen group and two (6%) in the treatment-naïve group.

Finally, another newly identified study¹⁰⁹ reported that, at baseline, 36/69 patients received NIV, while on treatment seven more patients started NIV.

Types 2 and 3

As mentioned in the previous MTA report, no participants in the nusinersen group required permanent ventilation during the trial period within the CHERISH trial.^{1,28} This pattern was consistent in CHERISH-related extension studies and in the NICE company submission based on NCT02462759.

Multiple types

A newly identified study¹¹⁸ reported that ventilatory support was required by six and two type 1 SMA patients at baseline and follow-up, respectively, and by two type 2 SMA patients at baseline and follow-up.

Newer data from Acsadi et al. (2021) reported a significant reduction in cumulative ventilation support time among nusinersen-treated patients compared to sham-treated controls.²⁹

MAA evidence

Paediatric registry

The results for this outcome are taken from the updated April 2025 report.

The registry defined permanent ventilation as any ventilation type for ≥ 16 hours/day continuously for > 21 days or tracheostomy. There was not enough data to conduct a formal analysis. Three patients have been permanently ventilated but details specifying when this happened are lacking for two of them. Another patient from the EAP, not included in the analysis due to lack of baseline data, was also on permanent ventilation. It is worth noting that these patients were part of the EAP and, therefore, had more chronic type 1 SMA. Compared to the natural history, where approximately 90% were either deceased or needing permanent ventilation, the number of patients represented in the MAA who needed permanent ventilation is very small number.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

No patients had events of permanent ventilation since commencing nusinersen treatment. It is worth noting that the registry reported descriptive statistics for lung function, which suggest stabilisation for type 2/3 non-sitters, sitters and walkers over the study period.

13.4.1.7 Stamina and fatigue

13.4.1.7.1 Individualized Neuromuscular Quality of Life Questionnaire (INQoL) - fatigue score

No evidence was reported by individual SMA type.

Multiple types

One newly identified study¹⁰¹ examined the effect of nusinersen on fatigue in individuals with different types of SMA type followed up at months 6, 10 and 14 using INQoL fatigue domain scores. The study reported a significant improvement in the fatigue domain of the INQoL scores throughout the follow-up periods ($P=0.0137$)

13.4.1.7.2 Fatigue

No evidence was reported by individual SMA type.

Multiple types

Two studies identified in the earlier review reported fatigue following nusinersen.^{209,226} One study reported increased fatigue during treatment,²²⁶ whilst the other reported improvement in fatigue.²⁰⁹

13.4.1.8 Mortality

SLR evidence

Presymptomatic

New final analysis data reported in the clinical study report (CSR) for the NURTURE study by Tichler et al. (2024) provide updated long-term survival outcomes for nusinersen in patients with genetically confirmed, presymptomatic 5q SMA. Survival status was assessed over the entire study period (from baseline to the last assessment, up to Day 2891—approximately eight years). No deaths were reported during the study, further supporting the long-term survival benefit of nusinersen in this patient population.^{175,176}

As noted in the previous report, the integrated analysis of the NURTURE and ENDEAR–SHINE studies investigated the continued benefit of nusinersen initiated presymptomatically. In this analysis, 100% survival was reported among the 25 children in the NURTURE cohort, with no deaths occurring over a median treatment duration of nearly four years.^{1,131}

As previously reported, an early-phase trial (NCT02386553) involving infants likely to present with type 1 or 2 SMA also reported complete survival at the five-year mark, with all 25 children alive at last follow-up.^{1,30} A subsequent evaluation by Crawford et al (2023), involving patients transitioning to long-term follow-up, reported complete survival over five years in all 25 participants.³⁰

Type 1

The ENDEAR study (NCT02193074) and its extension SHINE assessed nusinersen in infants with symptomatic type 1 SMA. According to Finkel et al (2021), and as mentioned in

the previous MTA report, approximately 75% of participants in cohort 2 remained alive at the last reported follow-up. The median time to death or permanent ventilation was longer in the nusinersen arm compared to controls.^{1,131}

New data from Arjunji et al (2019), comparing OA and nusinersen among patients with type 1 SMA, found that all participants in the OA group were alive during the 56-week follow-up period. Among the nusinersen-treated group, 66% of participants were reported to be alive during the same follow-up period.²²⁴ Another newly identified study¹¹⁵ reported that the numbers of patients who died following nusinersen treatment was 2/28 compared to 37/38 in a treatment-naïve group. An additional study,¹⁰⁹ also newly identified in this review, reported that four patients died due to causes considered non-related to the drug or lumbar puncture procedure.

Types 2 and 3

For types 2 and 3 SMA, mortality outcomes were drawn from the CHERISH study (NCT02292537) and associated analyses; no new data were reported. As noted in the previous review, the results reported by Mercuri et al (2018) showed no deaths in either the nusinersen or control groups during the 15-month follow-up period.^{1,28} These findings were consistent across other CHERISH-related analyses, including the CS2/CS12 cohorts (NCT01703988), in which no deaths were reported among participants.²⁰⁴

Multiple types

In an additional study by Acsadi et al (2021), one death occurred in the sham-treated group, while no deaths were reported among nusinersen-treated participants, although this study was not powered specifically for mortality outcomes.²⁹

MAA evidence

Paediatric registry

The results for this outcome are taken from the updated April 2025 report.

All patients who died were reportedly type 1 patients:





Adult registry

The results for this outcome are taken from the updated April 2025 report.

No occurrence of death occurred after starting nusinersen.

13.4.1.9 Adverse events

SLR evidence

It is noteworthy that most adverse events (AEs) reported across the included documents appear to be attributable to the underlying disease or the method of administration (e.g., lumbar puncture), rather than the treatment itself.

Presymptomatic

As noted in the NURTURE study population, comprising presymptomatic infants with genetically confirmed SMA, no adverse events led to treatment discontinuation in this target group. Safety outcomes remained favourable over the follow-up period.⁶⁸

New data from the final analysis reported in the CSR for the NURTURE study demonstrated that, over a follow-up period of up to Day 2891 (approximately eight years), there were no treatment-related discontinuations or deaths. Most adverse events were mild to moderate in severity, and no new safety signals emerged during long-term follow-up.^{175,176}

As reported in the previous MTA report, Darras et al (2019) observed that all participants experienced AEs, with common events including post-lumbar puncture syndrome (57%), headache (46%), respiratory tract infections (43%) and gastrointestinal complaints such as vomiting (21%). SAEs were reported in 18% of participants but none were considered to be related to treatment. No discontinuations occurred due to AEs and no laboratory abnormalities or neurological worsening were attributed to nusinersen.^{1,204}

As noted in the previous MTA report, Crawford et al (2023) followed infants at high genetic risk for SMA over an additional two years. No AEs were judged study-drug related, although 40% had AEs possibly linked to nusinersen. Most AEs were non-serious and consistent with underlying disease presentation, such as constipation and vomiting.^{1,228} All resolved without discontinuation except for isolated cases of proteinuria and clonus. Serious AEs occurred in 48% of participants, but none were considered drug-related^{1,228}

Type 1

According to the EMA (2023) and based on the findings of Finkel et al (2017; 2021), AEs were common in both nusinersen and control groups.^{27,68,131} The most frequently reported AEs included respiratory infections, feeding difficulties and constipation. Finkel et al (2017) reported that the overall AE incidence was similar between groups (96% in nusinersen vs. 98% in control), but the rate of severe AEs (56% vs. 80%), serious AEs (76% vs. 95%), and treatment discontinuation due to AEs (16% vs. 39%) was notably lower in the treatment group.²⁷

In follow-up analyses, Finkel et al (2021) reported that there were five deaths attributable to SMA and 101 SAEs in 80% of patients, although none of these were considered to be treatment-related. The incidence of respiratory and gastrointestinal AEs declined over time (from 69% to 20% and 63% to 30%, respectively).¹³¹

Type 1 previously treated with OA

New data from the RESPOND study, reported by Masson et al (2024), Proud et al (2024) and Kuntz et al (2023), details adverse events in children with type 1 SMA previously treated with OA. Masson et al (2024) reported that 82% (31/38) of participants experienced AEs, the most common being infections (63%) and respiratory disorders (26%). Two participants developed mild, treatment-related proteinuria, which resolved. Thirteen patients (34%) experienced serious AEs, none of which were attributed to nusinersen during the 183-day follow-up.¹⁰⁷

Proud et al (2024) reported that 82% of participants reported AEs. Infections and infestations were the most common (63.2%), followed by respiratory (26.3%), gastrointestinal (13.2%), general disorders including injection-site reactions (13.2%), and skin-related AEs (13.2%). Two mild AEs (proteinuria) were considered related to nusinersen but no serious AEs were drug-related. All AEs resolved during the median 230.5 day follow-up.²²³

Kuntz et al (2023) reported upper respiratory tract infections in six participants and viral upper respiratory tract infections in five. Mild proteinuria in two cases was identified as treatment-related but resolved. Nine serious AEs were reported, none of which were related to nusinersen. There were no deaths or post-lumbar puncture syndromes during the median 183-day follow-up.²²⁹

Types 2 and 3

As reported by the EMA (2023), in patients with SMA types 2 and 3, data from the CHERISH trial and its extensions served as the primary safety evidence.^{28,68} Mercuri et al (2018) reported that 93% of patients in the nusinersen group and 100% in the control group experienced AEs. SAEs occurred in 17% of nusinersen-treated participants compared to 29% of controls.²⁸

New data extracted from the SHINE study, as reported by Day et al (2020), confirmed that most adverse events were mild or moderate in severity and were primarily related to the underlying disease or to lumbar puncture procedures. Only one SAE (appendicitis) was reported, which was judged by investigators to be unrelated to nusinersen treatment.²¹⁹

Multiple types

Acsadi et al (2021), in a study of children excluded from ENDEAR and CHERISH, reported pyrexia, cough, pneumonia, and vomiting as the most frequent AEs. No treatment-related discontinuations occurred. One participant in the sham treatment arm withdrew due to AEs.^{29,68}

New data from Darras et al (2020) evaluated adverse event profiles across presymptomatic (NURTURE) and symptomatic (ENDEAR–SHINE) cohorts. In the NURTURE group (median follow-up: 33.9 months), the most frequently reported AEs were pyrexia (84%), upper respiratory tract infections (76%), and vomiting (40%). In the ENDEAR–SHINE cohort (median follow-up: 997.5 days), similar patterns were observed, with pyrexia (66%) and pneumonia (31%) among the most common events.²³⁰

Another study¹¹⁸ that was newly identified in this review reported that 10 patients experienced AEs, which included proteinuria, thrombocytosis and intracranial hypotension, though cessation of treatment was not required.

Unreported type

One study¹⁰⁷ reported that the overall number (%) of adverse effects that occurred in nusinersen recipients was 31/38 (82%). Of the 31 children who experienced adverse effects, infections/infestations occurred in 63% of the children, respiratory, thoracic and mediastinal disorders occurred in 26%, mild proteinuria in 5% and SAEs in 34%.

13.4.1.10 Health-related quality of life and Patient Reported Outcomes

SLR evidence

New data on health-related quality of life for patients with genetically confirmed 5q SMA and their caregivers have been identified in the studies detailed below. These findings—drawn from both presymptomatic and symptomatic populations—offer additional insights not previously captured in earlier evidence syntheses.

Presymptomatic

In the final analysis of the NURTURE study, health-related quality of life using the Pediatric Quality of Life Inventory (PedsQL) was reported in presymptomatic patients treated with nusinersen.^{175,176} Data collection was conducted between approximately day 1800 and day 2880. PedsQL scores, where available, indicated improvements in patients' mobility and overall quality of life, with many families reporting positive changes in daily functioning. However, substantial variability in HRQoL scores was observed over time.^{175,176}

Subgroup analysis by SMN2 copy number showed that participants with three SMN2 copies generally reported slightly higher median scores at certain time points, particularly in the Neuromuscular Module. A discrepancy was also observed between participant-reported and parent-reported outcomes: while participants with two SMN2 copies reported relatively stable scores between Day 1800 and Day 2880, their parents reported a decline in median total scores over the same period. These findings highlight the importance of capturing both self-reported and proxy perspectives when evaluating quality of life in SMA.^{175,176}

Types 2 and 3

Day et al. (2020) evaluated caregiver-reported outcomes in families of patients with SMA types 2 and 3 using the ACEND (Assessment of Caregiver Experience in Neuromuscular Disease) tool. Over a median follow-up period of approximately 1952 days [range: 1860–2121 days], most caregivers reported stable or improved scores across seven assessed domains, suggesting sustained or enhanced caregiver well-being during long-term nusinersen treatment.⁵⁵

13.4.1.10.1 EQ-5D-L

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report. It is important to note that data reported here is from a pilot study aiming to recruit 50 paediatric patients. There was insufficient data to assess separate groups (i.e. SMA type). Additionally, the limited amount of data means the results require cautious interpretation. Furthermore, pilot studies often do not present comparative data due to imprecision and unreliability.

Only two patient responses were recorded as being available for this outcome and therefore no data was presented.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The registry highlighted potential limitations of the PROMs evidence. The patient-reported nature of PROMs carries the risk of voluntary response bias and recall bias. PROMs data has been obtained from the registry and displayed in the report as a representation of a smaller proportion of the entire SMA population. As such, results must be interpreted with care.

Utilising a Pareto Classification of Health Change method, the registry reported whether patients' health status was better, worse, the same or mixed (i.e. better on one dimension but worse on another). Data was available with for 11 non-sitters with a baseline and a follow-up submission.

[REDACTED]

[REDACTED]

Table 94: Number of type 2/3 patients reporting changes in EQ-5D-L for nusinersen from the adult registry at each follow-up time point

Nusinersen adult EQ-5D-5L		Time point (n/N)								
Measure	Type	6 months	1 year	1.5 years	2 years	2.5 years	3 years	3.5 years	4 years	4.5 years
Better	2/3 non-sitters	■	■	■	■	■	■	■	■	■
Same	2/3 non-sitters	■	■	■	■	■	■	■	■	■
Mixed	2/3 non-sitters	■	■	■	■	■	■	■	■	■
Worse	2/3 non-sitters	■	■	■	■	■	■	■	■	■
Better	2/3 sitters	■	■	■	■	■	■	■	■	■
Same	2/3 sitters	■	■	■	■	■	■	■	■	■
Mixed	2/3 sitters	■	■	■	■	■	■	■	■	■
Worse	2/3 sitters	■	■	■	■	■	■	■	■	■
Better	2/3 walkers	■	■	■	■	■	■	■	■	■
Same	2/3 walkers	■	■	■	■	■	■	■	■	■
Mixed	2/3 walkers	■	■	■	■	■	■	■	■	■
Worse	2/3 walkers	■	■	■	■	■	■	■	■	■

Abbreviations: NR = Not Reported as data was not available for this time point; n = number of patients who met the criteria for that category; N = overall number of patients

13.4.1.10.2 EQ-5D-Y

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report. It is important to note that data reported here is from a pilot study aiming to recruit 50 paediatric patients. There was insufficient data to assess separate groups (i.e. SMA type). Additionally, the limited amount of data means the results require cautious interpretation.

Registry data were available for EQ-5D-Y total score and EQ-5D-Y-VAS. The total score had 27 patients with available data at first entry and nine with a follow-up (latest available; see Table 95). The limited data suggests maintenance of total score, with a higher score representing more problems experienced.

Table 95: Change in EQ-5D-Y total score for those receiving nusinersen; from Paediatric MAA report December 2023

	Number of patients	Mean	SD	Median	Min	Max
First entry	27	10.9	1.4	11	9	13
Latest available	9	11	1.8	12	8	13
Change first to last available visit	9	0.3	1.2	0	-1	3
Abbreviations: SD = standard deviation						

The EQ-5D-Y VAS was available for 33 patients at first entry. Twelve patients had a data point from with the latest available visit. The limited data suggests an overall decrease in VAS, which would indicate worsening health status (see Table 96). However, the limited interpretation of the data needs to be considered.

Table 96: Change in VAS for those receiving nusinersen; from Paediatric MAA report December 2023

	Number of patients	Mean	SD	Median	Min	Max
First entry	33	78.8	17.9	80	20	100
Latest available	12	79.6	15.5	82.5	50	100
Change first to last available visit	12	-5.3	16.0	-5.5	-25	20
Abbreviations: SD = standard deviation						

Adult registry

The adult registry did not provide evidence for this outcome.

13.4.1.10.3 *HRQoL measures from unreported tools*

SLR evidence

Multiple types

The original review identified eight studies assessing HRQoL in patients treated with nusinersen where the tool measured was not reported. Of these, four studies showed no significant difference as a result of nusinersen treatment on HRQoL,^{161,170,208,210,231} while three showed improvements compared to before nusinersen or to control group.^{121,232,233}

13.4.1.10.4 *PGI-S*

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report. It is important to note that data reported here is from a pilot study aiming to recruit 50 paediatric patients. There was insufficient data to assess separate groups (i.e. SMA type). Additionally, the limited amount of data means the results require cautious interpretation.

Initial visit data was reported for 32 patients. However, data was only available for 10 patients at the latest available visit. Of these 10 patients, six had no change in severity and four had a reduction of one unit. This limited data suggests maintenance or improvement for this PROM.

Adult registry

The results for this outcome are taken from the original April 2024 report.

The registry highlights potential limitations of the PROMs evidence. The patient-reported nature of PROMs carries the risk of voluntary response bias and recall bias. PROMs data have been obtained from the registry and displayed in the report as a representation of a smaller proportion of the entire SMA population. Results must be interpreted with care.

Data was only available for 15 type 2/3 patients at last follow-up, with 33 available at first entry. There was a rise in percentage of moderate and severe levels (45.45 to 46.67 and 36.3 to 40%, respectively). This suggests deterioration in the patient condition, though data is extremely limited. Additionally, the means of the baseline (3.18 ± 0.73) and last follow-up (3.27 ± 0.70) are similar. A sensitivity analysis was presented for those who had a PROM in ± 8 weeks visit window. This dataset had nine patients at last follow-up, with 22 patients available at first entry. Moderate level rose (27.7 to 33.3%), however severe level decreased (50 to 44.44%), representing improvement in patient condition. Additionally, the means of the baseline (3.27 ± 0.83) and last follow-up (3.22 ± 0.83) are similar. Unlike the paediatric registry, the adult registry did not report if the patients available at last entry available showed improvement, maintenance or worsening.

13.4.1.10.5 *PGI-I*

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report. It is important to note that data reported here is from a pilot study aiming to recruit 50 paediatric patients. There was insufficient data to assess separate groups (i.e. SMA type). Additionally, the limited amount of data means the results require cautious interpretation.

Initial visit data was reported for 35 patients. However, data was only available for 13 patients at the latest available visit. Of these 13 patients, seven had no change in improvement level. Worsening on the scale was experienced by two patients, one had a reduction of one unit, and another had a reduction of three units. Three had an improvement of one unit and one an improvement of two units. This limited data suggested mixed results for this PROM.

Adult registry

The results for this outcome are taken from the original April 2024 report.

The registry highlighted potential limitations of the PROMs evidence. Due to their patient-reported nature, PROMs hold the risk of voluntary response bias and recall bias. PROMs data has been obtained from the registry and displayed in the report as a representation of a smaller proportion of the entire SMA population. Results must be interpreted with caution.

Data was available for 49 type 2/3 patients at first entry and 38 at last follow-up. There was an increase in the proportion of people reporting they were much improved, minimally improved, had experienced no change, or were minimally worse. This coincided with a decrease in the proportion of patients ranking as much worse and very much worse, which suggests an overall improvement. Additionally, the means at baseline (3.63 ± 1.35) and last follow-up (3.50 ± 1.13) are similar but show a small decrease on average. A sensitivity analysis was presented for those who had a PROM in the ± 8 week visit window. This dataset had 30 patients at last follow, with 43 patients available at first entry. Proportions of much improved and minimally improved decreased between the two data points. While proportions of no change and minimally worse increased. Proportions of much worse and very much worse decreased. Overall, it appears that the condition was slightly better or similar. Additionally, the means of the baseline (3.39 ± 1.33) and last follow-up (3.53 ± 1.11) are similar, with a slight increase. Unlike the paediatric registry, the adult registry did not report if the patients available at last entry available showed improvement, maintenance or worsening.

13.4.1.10.6 Egen Klassifikation-2 (EK-2)

SLR evidence

Type 1

The original review identified one study examining EK2 in type 1 SMA patients treated with nusinersen, reporting that 5/41 patients showed a change of at least two points.¹³³

Type 2/3

The original review identified one study examining EK-2 in patients with type 2/3 following nusinersen treatment, reporting improvement by at least two points in five patients.²³⁴

Multiple types

The original review identified one study examining EK-2 in people with different types of SMA following nusinersen treatment, showing a significant increase.¹⁶⁹

*MAA evidence***Paediatric registry**

The results for this outcome are taken from the updated April 2025 report.

The EK-2 scale assesses activity and participation in individual with non-ambulatory SMA. The scale covers eight daily life categories including wheelchair use and transfers, trunk mobility, eating, swallowing, breathing, coughing and fatigue. A higher EK-2 score indicates a greater level of functional impairment. No formal analysis was conducted and individual participant data was provided in graphical format. Most individuals maintained their level of function. Type 1 patients showed a trend towards improvement. However, some patient scores increased (i.e. worsened) over time. Data was not available for type 1 non-EAP. It is important to note that this data was not mandated and has not been cleaned to the same degree as mandated items.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The adult registry conducted MRMMs for type 2/3 non-sitters and sitters. For non-sitters the mean change suggested improvement. There was minimal data with short follow-up due to the number of patients available. No statistical significance was observed but the numerical trend of improvement suggests potentially positive outcomes for these patients. The limited data suggests potential improvement but should be interpreted with caution due to lack of data, with 13 patients available at baseline and five available at 2.5 years follow-up.

Similar results are observed in the patients classified as sitters, with no statistically significant changes occurring but the numerical trend suggesting maintenance or small improvements in EK-2 scores over time. At baseline data for 34 patients were available and five patients had data at 4 year follow-up. As with other outcomes, the data is sparser the longer the follow-up.

*13.4.1.10.7 SMA Independence Scale-Upper Limb Module (SMAIS-ULM)**SLR evidence***Type 2/3**

One newly identified study²¹⁹ reported data from the SHINE trial for the effects of nusinersen on SMAIS-ULM scores on types 2-3 SMA, reporting stable scores in three out of five participants (i.e. 0 point change).

*MAA evidence***Paediatric registry**

The results for this outcome are taken from the original December 2023 report.

It is important to note that data reported here is from a pilot study aiming to recruit 50 paediatric patients. There was insufficient data to assess separate groups (i.e. SMA type). Additionally, the limited amount of data means the results require cautious interpretation.

Table 97 shows data at first entry to the patient registry whilst on nusinersen and for the most recent visit. In addition, a summary of changes from first to last available assessment is shown. Where individual items are missing, an adjustment was been made to the total score so that

the total is expressed out of the total number of items (similar to the approach for motor outcomes).

Table 97: Change in SMAIS for patients on nusinersen treatment; from Paediatric MAA report December 2023

	Number of patients	Mean	SD	Median	Min	Max
First entry	31	21.4	11.2	21	4	44
Latest available	11	25.6	8.9	25	9	44
Change first to last available visit	11	1.6	4.4	2	-8	7
Abbreviations: MAA = Managed Access Agreement; SMAIS = Spinal Muscular Atrophy Independence Score; SD = standard deviation						

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The registry highlighted potential limitations of the PROMs evidence. The patient-reported nature of PROMs carries the risk of voluntary response bias and recall bias. PROMs data has been obtained from the registry and displayed in the report as a representation of a smaller proportion of the entire SMA population. Results must be interpreted with caution.

The registry reported whether type 2/3 patients reported an increase, the same, or decrease in the SMAIS-ULM. Data was available with for nine non-sitters, with baseline and follow-up submissions.

. For a breakdown over the follow-up period see

Table 98.

Table 98: Number of type 2/3 patients reporting changes in SAMIS-ULM for nusinersen from the adult registry at each follow-up time point

Nusinersen adult SMAIS-ULM		Time point (n/N)							
Measure	Type	6 months	1 year	1.5 years	2 years	2.5 years	3 years	3.5 years	4 years
Increased	2/3 non-sitters	■	■	■	■	■	■	■	■
Same	2/3 non-sitters	■	■	■	■	■	■	■	■
Decrease	2/3 non-sitters	■	■	■	■	■	■	■	■
Increased	2/3 sitters	■	■	■	■	■	■	■	■
Same	2/3 sitters	■	■	■	■	■	■	■	■
Decrease	2/3 sitters	■	■	■	■	■	■	■	■
Increased	2/3 walkers	■	■	■	■	■	■	■	■
Same	2/3 walkers	■	■	■	■	■	■	■	■
Decrease	2/3 walkers	■	■	■	■	■	■	■	■

Abbreviations: SMAIS-ULM = Spinal Muscular Atrophy Independence Scale-Upper Limb Module; n = number of patients meeting this criterion; N = overall number of patients; NR = not reported as data was not available for this time point

13.4.1.10.8 Impact on carers and families

13.4.1.10.9 SLR evidence

No evidence was reported for carers of presymptomatic or type 1 patients.

Types 2 and 3

The current review identified three studies that reported the impact of nusinersen on ACEND.^{122,219} One trial reported longer term outcomes for five adolescent patients with type 2/3 SMA. Most caregivers reported to be stable or improved in all seven domains of the ACEND.²¹⁹ One comparative prospective study showed no statistically significant differences of the score between or within both groups between baseline and 12-month follow-up (nusinersen n = 16; standard of care n = 26).¹²²

13.4.1.10.10 Pediatric Quality of Life Inventory (PedsQL)

SLR evidence

No evidence was reported for presymptomatic or type 1 patients.

Types 2 and 3

The original review identified two studies assessing PedsQL changes when patients received nusinersen. No significant change in the PedsQL were reported in either study.^{164,235}

13.4.1.10.11 SF-36

SLR evidence

No evidence was reported according to individual SMA type.

Multiple types

The original review identified one study assessing the impact of nusinersen treatment on the SF-36. The study showed a change of -4.8 points on the SF-36 scale.²²⁶

13.4.1.10.12 Individualized Neuromuscular Quality of Life (INQoL)

SLR evidence

No evidence was reported according to individual SMA type.

Multiple types

The current review identified one study assessing the impact of nusinersen treatment on INQoL.¹⁰¹ This retrospective cohort study of 78 patients showed statistically significant lowering of scores (i.e. improved quality of life) from baseline to 14 months for the over INQoL score and weakness score. No statistically significant differences were observed for INQoL total score or weakness score between walkers and on-walkers, with both groups showing decreases (improvements) over time.¹⁰¹

13.4.1.10.13 Ability to socialise

SLR evidence

No evidence was reported according to individual SMA type.

Multiple types

The current review identified two studies that assessed socialisation in patients with different types of SMA receiving nusinersen, both of which were retrospective cohorts.^{101,180} One study assessed children's (n = 16) social integration via interview.¹⁸⁰ After three years of nusinersen treatment, 11 of 16 children socialised in school or daycare. Four of the five children who did not socialise were non-invasively ventilated and/or had gastrostomy, whereas the socialised children were free of ventilatory and nutritional support.¹⁸⁰ The other study provided data from the INQoL social relationships sub theme, which was measured at baseline (n=70), 6 months (n=48), 10 months (n=41) and 14 months (n=30). They observed an initial increase in the subscale score from baseline to 6 months (24 vs 32, respectively), however the results at 10 months (sub score: 21) and 14 months (sub score: 24) showed a statistically significant reduction from baseline.¹⁰¹ A lower score is to be interpreted as improved socialisation, with a higher score suggesting more issues within the subscale.

13.4.1.10.14 *Impact on Activities of Daily Living (ADLs), Independence and Emotions* SLR evidence

Presymptomatic

New final analysis data from NURTURE (2024) demonstrate that presymptomatic patients with genetically confirmed 5q SMA treated with nusinersen were able to achieve and maintain key markers of independence, particularly independent ambulation—an outcome rarely observed in untreated SMA. Of the 25 participants, 23 (13/15 with two SMN2 copies and all 10 with three SMN2 copies) achieved independent walking, with median ages of 23.7 months and 13.7 months, respectively. Additionally, retrospective comparison with seven untreated siblings (all with two SMN2 copies) highlighted substantial differences in disease progression: none of the siblings were able to sit or walk independently, four required ventilation, and four died. These findings reinforce the significant impact of early nusinersen treatment on functional independence and developmental outcomes in presymptomatic SMA.^{175,176}

Multiple types

The current review identified one study assessing ADLs, employment and independence for mixed type SMA patients treated with nusinersen.¹⁰¹ The INQoL activities sub theme, which was measured at baseline (n=70), 6 months (n=48), 10 months (n=41) and 14 months (n=30), showed a statistically significant reduction from baseline. The study showed a decrease at each follow-up time point for the subscale score: baseline was 59.5 points, 6 months 57.2 points, 10 months was 53.6 points, and 14 months was 50.4 points. The same pattern was observed when considering a subgroup of walkers and non-walkers, which showed a statistically significant reduction in score.¹⁰¹ A lower score is to be interpreted as improved socialisation, with a higher score suggesting more issues with that sub scale.

Similarly, for the independence subscale there was a statistically significant reduction from baseline to follow-up (baseline: 59; 6 months: 54.8; 10 months: 54.3; 14 months: 50.8 points). This finding did not extend to the subgroup analysis of walkers and non-walkers, where there was a numerical trend of decreasing scores but this was not statistically significant.¹⁰¹

The same study showed a statistically significant reduction in the emotional impact sub scale.¹⁰¹ Specifically at baseline the score was 32 points, 6 months it was 29 points, 10 months 28 points, and 14 months it was 27 points.¹⁰¹ Similar results were observed for body image

(baseline: 54.8; 6 months: 50.1; 10 months: 46.5; 14 months: 46.7 points), which also was recorded as having a statistically significant reduction.¹⁰¹

13.4.1.11 *Other outcomes*

13.4.1.11.1 *Clinical Global Impression-Improvement scale (CGI)*

SLR evidence

No evidence was reported according to individual SMA type.

Multiple types

The previous review identified three studies which presented evidence for the Clinical Global Impression-Improvement scale (CGI-I) in people with different types of SMA type receiving nusinersen.^{29,169,200} One study examined CGI-I following nusinersen in type 1 and 2 patients. More patients receiving nusinersen improved compared to those initially in the sham condition (EMBRACE).²⁹ One of the other studies reported that 62.3% of patients' scores improved and 37.7% were unchanged;²⁰⁰ 64.1% and 61.5% treated patients improved in the other study.¹⁶⁹

13.4.2 Risdiplam

13.4.2.1 Motor function

Three studies reported motor function outcomes for risdiplam: RAINBOWFISH for patients with presymptomatic SMA,^{58,68} FIREFISH for type 1 patients,^{54,55} and SUNFISH for types 2/3 patients.^{47,49,50} This updated review contains newly published data for each of these studies, which suggests most patients continued to improve or maintained their motor function in all measured outcomes up to two years (presymptomatic), three years (type 1) and five years (types 2/3).

████████████████████ Data for type 2/3 SMA were also reported in two prospective studies,^{153,155} as well as one retrospective single arm study.¹⁴⁹ Only 1 of 85 patients across these three studies declined in RULM score at 16 months. No published data was found for WHO Motor Milestones or ATEND outcomes in studies reporting on risdiplam, though MAA data was available for both.

MAA evidence was available for some outcomes from the original December 2023 report and as an updated report obtained in April 2025 from both paediatric and adult registries. Much of the paediatric data is limited but is reported alongside the adult data below. From the adult data, most patients improved or maintained their motor function as measured by RULM, 6MWT, WHO Motor Milestones, HINE-2 and ATEND. For type 2/3 sitters, there was a trend to worsening RHS outcomes after a year.

13.4.2.1.1 WHO Motor Milestones

None of the SLR evidence reported on WHO motor milestones.

MAA evidence

Paediatric registry

The data for the WHO MM was updated by the paediatric registry in April 2025 from the original submissions in December 2023.

WHO MM data for risdiplam in the paediatric registry MAA was reported in a manner dissimilar to that for nusinersen (see Section 13.4.1.1.1). The data is reported by SMA type and, within each type, the number of patients in each classification (e.g. non-sitters, sitting without support, crawling) for baseline and every 6 months up to 3 years. Information regarding attaining or maintaining is not directly reported and challenging to disentangle.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

All type 1 patients remained non-sitters from baseline throughout the follow-up timepoints.

Type 2/3 patients were categorised by status of either non-sitter, sitter, or walker. For non-sitters,

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[REDACTED]
[REDACTED]
[REDACTED], see

Table 99.

The registry provided further context to the results by stating the results are like natural history in the adult SMA population. They show maintenance with limited transition between functional groups.

[REDACTED]

[REDACTED] The stability captured on the WHO motor scale demonstrates the known stability of this group. However, it is important to note the lack of sensitivity of this scale, as it does not capture important subtle changes. For example, the sitters group can score 1-5 on the WHO motor scale and not change classification. Therefore, a change from sitter to walker implies a significant change in their motor function, [REDACTED].

Table 99: Risdiplam adult registry WHO MM attainment or maintenance of motor milestones

Risdiplam adult WHO MM		Time point (n/N)								
Measure	Type	6 months	1 year	1.5 years	2 years	2.5 years	3 years	3.5 years	4 years	4.5 years
Attainment of a motor milestone	1	■	■	■	■	■	■	■	■	■
Attainment of a motor milestone	2/3 non-sitters	■	■	■	■	■	■	■	■	■
Attainment of a motor milestone	2/3 sitters	■	■	■	■	■	■	■	■	■
Attainment of a motor milestone	2/3 walkers	■	■	■	■	■	■	■	■	■
Maintenance of a motor milestone	1	■	■	■	■	■	■	■	■	■
Maintenance of a motor milestone	2/3 non-sitters	■	■	■	■	■	■	■	■	■
Maintenance of a motor milestone	2/3 sitters	■	■	■	■	■	■	■	■	■
Maintenance of a motor milestone	2/3 walkers	■	■	■	■	■	■	■	■	■

Abbreviations: WHO MM = World Health Organization Motor Milestones; n = number of patients who met criteria; N = number of patients overall; NA = Not Applicable (due to no data being available for this time point); NR = Not Reported as there is no data for this time point; *one patient's status was unknown

13.4.2.1.2 CHOP-INTEND

SLR evidence

Presymptomatic SMA

Results extracted for this review update from the single arm (uncontrolled) RAINBOWFISH study showed that patients achieved high levels of motor function prior to month 12 on the CHOP-INTEND, with 10 of 13 patients (76.9% of patients analysed) achieving scores of ≥ 60 at month 4 (week 16). Four of 7 patients achieved the maximum score of 64 at month 12.⁶⁸

Type 1

Results were extracted for this review update from three uncontrolled studies reporting the effects of risdiplam on CHOP-INTEND score. The FIREFISH study reported an increase in the proportion of infants achieving a CHOP-INTEND score of at least 40 points by month 12. After 12 months of treatment, 23 out of 41 infants (56%) achieved a CHOP-INTEND score of 40 or higher.⁵⁴ Additionally, 37 out of 41 infants (90%) showed an increase of at least four points from baseline in the CHOP-INTEND score. The proportion of infants who achieved an increase of at least four points from baseline on the CHOP-INTEND was maintained at month 24.⁵⁴ At the 36-month follow-up, 78% (36/46) of participants achieved a CHOP-INTEND score ≥ 40 .⁵⁵ At 5-year follow-up, 81% achieved a score of ≥ 40 and 62% attained a score of ≥ 50 .⁵⁶

Types 2 and 3

No evidence was reported for types 2 and 3 SMA.

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report.

An MRMM was not possible for CHOP-INTEND for type 1 patients due to limited data. Data from eight patients were available for this outcome. The mean scores suggest improvement over time. However, due to small number of patients and lack of statistical analysis, the interpretation of these results is limited.

Adult registry

This outcome is not applicable for adult patients as CHOP INTEND is used for children aged 1-38 months.¹⁹⁸

13.4.2.1.3 HINE-2

SLR evidence

Presymptomatic

Two records, one that was cited in the earlier review⁶⁸ and a newly included study,⁶⁰ reported data from the uncontrolled RAINBOWFISH trial. Outcome data were reported for the 12 month follow-up in both records. Data from one record⁶⁸ suggested that all participants (n=7 participants for which data were available out of 18 enrolled) developed motor abilities, including the ability to sit without support. The other record⁶⁰ reported that 24/26 infants (92%) were able to sit without support, 21/26 (81%) were able to stand and 16/26 (62%) were able to walk.

Type 1

Three records, including two that were included in the earlier review,^{54,236} and one newly identified record,⁵⁵ reported data from the FIREFISH single arm trial. The results from one record²³⁶, as reported in the original review, suggested that patients demonstrated an overall increase in HINE-2 score, with higher doses leading to higher proportions of responders and more patients with greater head control at the 12-month follow-up. The results from another record,⁵⁴ also reported in the original review, indicated an increased number of patients achieving the highest motor milestone category at the 24-month follow-up. Additional data extracted from the same study for this review update showed that, although no infants could walk or stand independently at month 24 following treatment initiation, more infants achieved a higher motor milestone category in the HINE-2 compared with month 12. For example, more infants achieved “standing with support” and one infant (2% of the sample) achieved “cruising.” Furthermore, more infants were reported to be able to achieve the highest motor milestone category. For instance, more infants were able to “pivot (rotate)” as recorded within the sitting milestone, more infants were able to “roll from supine to prone”, and two infants were recorded for the crawling milestone as able to “crawl on their hands and knees” at month 24 compared to month 12.

Results from another record,⁵⁵ from which data were extracted for this review update, showed that the following numbers and proportions of participants achieved milestones from the HINE-2 assessment at 24 months: head control (37/58 participants, 64%); sitting (16/58 participants, 28%); rolling (23/58, 40%); standing (7/58, 12%); and walking (1/58, 2%). Between months 24 and 36, the numbers of participants who gained, maintained and lost each skill out of 49 participants for whom data were available were: 3 gained, 36 maintained and 0 lost for head control; 2 gained, 4 maintained and 2 lost for sitting; 3 gained, 22 maintained and 0 lost for rolling; 5 gained, 6 maintained and 1 lost for standing; and 2 gained, 1 maintained and 0 lost for walking.

The FIREFISH study reported that, at five years, 69% of children achieved head control (compared to 47% before), 59% achieved sitting (including stable sit and pivot, previously 28%), 50% could roll supine to prone (10%), 12% could stand (aided or unaided, previously 3%), and 10% were cruising where previously none had.⁵⁶

No evidence was reported for types 2 and 3 SMA.

MAA evidence

Paediatric registry

The results for this outcome are taken from the updated April 2025 report.

There was insufficient data to conduct an MRMM in the type 1 patients for this outcome. However, the proportion of patients in type 1 and types 2/3 showing improvement (i.e. a 1-point increase in the HINE-2 score) was reported (see Table 100). The registry provided some context for this data, stating it was noticeable with longer follow-up that maintenance, and in some cases improvement, are documented. This may show long lasting treatment effects, even with expected disease progression (i.e. increased contractures or scoliosis). The natural history of SMA is characterised by progressive deterioration in motor function, as well as respiratory and bulbar function. This will be more rapid in SMA type 1 but will inevitably happen in SMA type 2 and 3 as well. Stabilisation needs therefore to be considered a treatment effect, leading to better long-term outcomes and quality of life. Even in this heterogeneous cohort of

real-world data, where patients started treatment when heavily symptomatic and chronically affected by the disease, there is a clear treatment effect resulting in stabilisation.

Table 100: Proportion of patients achieving a 1 point increase in HINE-2 at latest visit, adapted from the updated (April 2025) paediatric MAA report

	Type 1	Type 2/3 non-sitters	Type 2/3 sitters/walkers
N			
No improvement			
1 point increase			
> 1 point increase			
Missing			
Abbreviations: HINE-2 = Hammersmith Infant Neurological Examination; MAA = Managed Access Agreement			

Adult registry

This outcome is not applicable for adult patients as HINE-2 is used for children aged 2-24 months.¹⁹⁸

13.4.2.1.4 BSID-III

SLR evidence

Presymptomatic

New data from a 12-month follow-up of the uncontrolled RAINBOWFISH study showed that, at month 12, 80% of infants (n=5) were able to sit without support for ≥ 5 seconds, and 7/8 infants with two SMN2 copies were able to sit without support for ≥ 30 seconds, including all infants with CMAP amplitude < 1.5 mV (n=3).⁶⁰

Type 1

New data from the uncontrolled FIREFISH study, reported that, after 24 months of treatment, all 12 infants who had previously attained the ability to sit without support for ≥ 5 seconds at month 12 maintained this ability.⁵⁴ Additionally, at month 24, 35 (60%) of infants met the endpoint of sitting without support for ≥ 5 seconds, 23 (40%) of infants were sitting without support for ≥ 30 seconds, and 18 infants (44%) were able to sit without support for at least 30 seconds. However, no infants could stand alone or walk alone after 24 months of treatment. New data showed that, up to 36 months, four infants gained sitting without support for at least 5 seconds, 32 infants maintained this and none lost from 24 months measurement.⁵⁵ Furthermore, 15 infants gained sitting without support ability for at least 30 seconds, 20 infants maintained this ability and 0 lost this ability from the 24-month measurement. At five years, the FIREFISH study reported that 62% and 59% of children could sit without support for five and 30 seconds, respectively (previously 33% and 19%), while 7% of them achieved standing without support (previously 0%).⁵⁶

No evidence was reported for types 2 and 3 SMA.

13.4.2.1.5 MFM32

SLR evidence

No evidence was reported for presymptomatic SMA.

Type 1

According to newly identified data from the uncontrolled FIREFISH study, at month 12 the greatest improvement from baseline with risdiplam compared to placebo was observed in the youngest patients aged 2 to < 6 years, followed by those aged 6 to 11 years, and then those aged 12 to 17. No improvement from baseline in MFM32 was observed in the oldest patients, aged 18 to 25.⁵⁴

Types 2 and 3

Ten records, six of which were included in the earlier review^{23,83,229,237-239} and four which were newly identified,^{49,50,53,44} reported data from the SUNFISH RCT (RoB assessment: some concerns). The results from the earlier review reported that the MFM32 total score from baseline increased by 1.8 (95% CI: 0.7–2.9); 58% of patients experienced stabilisation (change of ≥ 0) and 32% achieved an improvement (change of ≥ 3) in MFM32 total score after 24 months of risdiplam treatment.^{229,237} Amongst patients initially assigned to the placebo group, change from adjusted baseline (month 12, before switching to risdiplam) in MFM32 total score was 0.3 (95% CI –0.7 to 1.3) after 12-months of risdiplam treatment; 59% experienced stabilisation, and 16% demonstrated improvement (change of ≥ 3) in MFM32 total score at month 24. Newly extracted data showed a statistically significant difference in change from baseline in MFM32 total score at month 12 in patients treated with risdiplam (n = 120) versus placebo (n = 60), favouring risdiplam.^{49,50} The gains observed with risdiplam treatment at month 12 were maintained between months 12 and 36. Other newly identified outcome data from the SUNFISH trial in the initial submission⁴⁴ and another study⁵³ reported mean change from baseline in MFM32 total score of -0.08(7.38) at 60 months and of these patients, 52.1% (49/94) achieved a change of ≥ 0 and 31.5% (33/94) achieved an improvement of ≥ 3 in MFM32 total score. The evidence further showed that though, there was an initial increase in change in baseline MFM32 total score, it remained stable generally in in trial participants compared to a sharp decline observed in an untreated population from the MFM-Lyon database.

Multiple types

As reported in the earlier review, the results from JEWELFISH study showed stabilisation of the MFM32 total score from baseline (mean total score = 39.93, 95% CI 37.07–42.80) to month 12 (mean total score = 40.41, 95% CI 37.30–43.52) and month 36 (mean total score = 40.67, 95% CI = 37.60–43.74).⁶²

13.4.2.1.6 HFMSE

SLR evidence

No evidence was reported for presymptomatic or type 1 SMA.

Types 2 and 3

Data reported in the earlier review from the SUNFISH RCT (RoB assessment: some concerns) showed a mean change from baseline in total HFMSE score at month 12 of 0.95 for the

intervention group, with a treatment difference of 0.58 in favour of risdiplam versus placebo.^{47,48,237} Recent studies report that these increases were sustained between months 12 and 36 in the risdiplam arm.^{49,50} The original review also reported that 22.6% of patients improved on at least one motor scale,¹⁵⁵ whilst a new study reported that "clinical stability in motor function was observed" based on the HFMSE and RULM.¹⁴⁹

Other newly identified outcome data from the SUNFISH trial in the initial submission⁴⁴ and another study⁵³ showed that participants followed up for 5 years, including those who received placebo for 12 months followed by risdiplam for 4 years, had HFMSE total scores that increased up to year 2 but returned to baseline by year 4. The mean change from baseline in HFMSE total score was -0.77(6.96) with 48.4% (46/95) of these participants achieving a change of ≥ 0 and 30.5% (29/95) achieving an improvement of ≥ 2 in HFMSE total score. Additionally, 49(40.8%) participants receiving risdiplam, 25 (41.7%) placebo and 74(41.4%) of All SUNFISH participants had HFMSE total score of < 10 .

Multiple types

As reported in the original review, in the JEWELFISH study the HFMSE total score was stable at month 24 compared with baseline (mean change from baseline in HFMSE total score: -0.11, 95% CI -0.98 to 0.76).⁶²

13.4.2.1.7 RULM

SLR evidence

No evidence was reported for presymptomatic or type 1 SMA.

Types 2 and 3

The SUNFISH RCT (RoB assessment: some concerns) reported significant improvements in RULM score at 12 months.^{47,48,237} New SUNFISH evidence extracted for this review update reported that motor function increases (including RULM) were sustained at the 36 month follow-up.^{44,49,50, 53}

Of two further studies that were reported in the original review, one showed no significant improvements at 12 months¹⁵³ and the other showed increases of more than 1 point in 5 patients and decreases in one patient at 16 months.¹⁵⁵

A newly identified uncontrolled study reported that, at the eight month follow-up, "clinical stability in motor function was observed" based on assessments using the HFMSE and RULM tools.¹⁴⁹

Newly identified outcome data from the SUNFISH trial in the initial submission⁴⁴ and another study⁵³ showed that the mean change from baseline in RULM total score was 2.11 at 5 years with 63.3% (62/98) of these participants achieving a change of ≥ 0 and 48% (37/98) achieving an improvement of ≥ 2 in RULM total score. Additionally, in participants followed up for 5 years including those who received placebo for 12 months followed by risdiplam for 4 years, the mean total RULM score was 19.7 (7.2) in those who received risdiplam, 20.9 (6.4) in placebo and 20.1 (7.0) across All SUNFISH participants.

Multiple types

As reported in the earlier review, data from the 24 month follow-up of the JEWELFISH study showed functional stabilisation of upper limb ability, assessed using the RULM, with a mean change of 0.71 (95% CI -0.17 to 1.26).⁶²

13.4.2.1.8 MAA evidence**Paediatric registry**

The results for this outcome are taken from the original December 2023 report.

An MRMM was not plausible for the type 1 patients in this outcome due to limited data. Data from nine patients were available for the RULM. The mean scores are uninformative due to variation and low patient numbers. From baseline, there is an initial drop at six months' follow-up (11.8 vs 9.1, respectively) in seven patients. At 1 year and 1.5 years, only one patient is available at each time point. Interpretation of these results is therefore extremely limited.

MMRM was possible for type 2/3 patients. The interaction between visit and baseline RULM score was not statistically significant. The analysis suggests some improvement from baseline at six months, with maintenance for the remaining two time points (1 and 1.5 years).

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The registry conducted MMRM for type 2/3 non-sitters and sitters. For non-sitters, from the baseline including 70 patients, there was an increase from baseline observed to 2.5 years (n=13). The mean change suggests improvement but no statistical significance is observed. However, the numerical trend of improvement suggests potentially positive outcomes for these patients. For sitters, the baseline data included 84 patients, of which 16 had data with a 2.5 year follow-up. No statistically significant changes occurred but the numerical trend suggests maintenance or small improvements in RULM scores over time.

13.4.2.1.9 6MWT**SLR evidence**

No evidence was reported for presymptomatic or types 1 or 2 SMA.

Type 3

As reported in the earlier review, the JEWELFISH study reported that, of 13 ambulant patients at baseline aged ≥ 6 years, all maintained their ability to walk. Among eight patients aged ≥ 6 years who were ambulant at baseline, previously treated with nusinersen, and evaluated both at baseline and at month 24, there was a mean increase in the total distance walked of 30.88 metres (95% CI -5.54 to 67.29).⁶²

MAA evidence**Paediatric registry**

The paediatric registry did not report on this outcome. However, the 10 metre run test was conducted as part of the RHS, results of which can be seen in Section 13.4.2.1.11.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

For type 2/3 walkers there were 24 patients at baseline and at 2.5 years follow-up data were available for six patients. The numerical trend suggests improvement over the follow-up period, with an initial increase that is maintained over time. Data is limited in the longer follow-

up periods. However, maintenance may be represented in the results, and this should be considered a good outcome.

13.4.2.1.10 CMAP amplitude

SLR evidence

Presymptomatic

One record, which reported results from the RAINBOWFISH trial and was included in the earlier review, reported an increased CMAP in 5/7 patients after 12 months.⁶⁸

No evidence was reported for types 1, 2 or 3 SMA.

13.4.2.1.11 RHS

SLR evidence

No evidence was reported for presymptomatic or type 1 SMA.

Types 2 and 3

One study¹⁵⁵ included in the original review reported an increase in RHS score for 2/6 patients, a meaningful improvement in three patients and a decrease of one point for one patient after 16 months.

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report.

An MRMM was not plausible for the type 1 patients for this outcome due to limited data. Nine patients' data were available for this outcome. The mean scores suggest improvement over time. At the 1 year follow-up, the mean score drops from baseline (5.0 vs 6.4, respectively), though this data is from only one patient. Due to the small number of patients and lack of statistical analysis, the interpretation of these results is limited.

An MMRM was possible for type 2/3 patients. The interaction between visit and baseline RULM score was not statistically significant. The analysis suggests no statistically significant changes from baseline to 1.5 years follow-up. These results imply that maintenance may be occurring, which should be considered a good outcome.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The adult registry conducted MMRMs for type 2/3 sitters and walkers. For sitters, the baseline included 19 patients and, for 1 year follow-up, eight patients had data. No statistical significance was observed, though the numerical trend suggests potential worsening of this outcome for these patients at 1 year. Data is limited and should be interpreted with caution. For walkers, the baseline data includes 24 patients and at 2.5 years follow-up six patients had data. The numerical trend suggests improvement over the follow-up period, with an initial increase that is maintained over time. Data is limited for the longer follow-up periods. However, maintenance may be represented and this should be considered a good outcome.

13.4.2.1.12 *ATEND*

No SLR evidence was found reporting ATEND as an outcome.

MAA evidence

Paediatric registry

The paediatric registry did not report on this outcome. The intended age range for this tool is still to be confirmed.¹⁹⁸

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The adult registry reported an MMRM for ATEND left and right in type 2/3 non-sitters and sitters. For non-sitters, at baseline 48 patients were included the analyses and six had data at the 36-month follow-up. The mean change suggests maintenance in the ATEND, with no statistically significant reductions or increases from baseline. Data is limited in the longer-term follow-up (i.e. 30 and 36 months; < 20 patients). The registry also noted an unusual asymmetry between the left and right ATEND, which has not been previously observed in large cohort studies.

The ATEND was utilised in sitters who were less functional patients (RHS < 6); these individuals show an unusual degree of symptomatic progressions. The baseline included 61 patients, with seven being followed up to 2.5 years. The results show no statistically significant reductions in improvement and numerical trends show maintenance with some potential improvements. However, patient numbers are limited in the later follow-up timepoint.

13.4.2.2 *Bulbar function*

SLR evidence

Presymptomatic

Data from the RAINBOWFISH trial indicated that most participants with presymptomatic SMA maintained their ability to feed orally following risdiplam treatment. A new study reported that, 8.5 months following initiation of risdiplam, all newborns following positive newborn screening or prenatal testing for SMA were alive and without feeding support.¹⁴⁸

Type 1

The FIREFISH study reported improved swallowing following risdiplam treatment.²³⁶ Another found that, over the course of the study, there was an improvement in ability to feed orally. At month 12, 34 infants (82.9%) were able to feed orally, which increased to 35 (85%) by month 24, while no infant lost the ability to swallow.⁵⁴

New data showed that 50/52 infants were alive at the 12-month follow-up and were able to swallow; at 36 months the numbers of infants who gained, maintained and lost the ability to swallow were 0, 48 and 1, respectively.⁵⁵ Also at 36 months, the numbers of participants who gained, maintained and lost the ability to feed orally were 1, 33 and 2 respectively (out of 50 participants), whilst 2, 28 and 1 participants gained, maintained and lost the ability to exclusively feed orally respectively (out of 38 participants). At five years, the FIREFISH study reported that 96% were able to swallow (compared to 94% beforehand), while the number

feeding orally had stayed at 91%, and the number feeding exclusively orally had risen from 76% to 80%.⁵⁶

No evidence was found for types 2 or 3 SMA.

13.4.2.3 Hospitalisation

SLR evidence

Presymptomatic

RAINBOWFISH reported that there were no overnight hospitalisations for presymptomatic patients.⁶⁸ There was no new evidence for hospitalisation in presymptomatic patients.

Type 1

Data from FIREFISH showed that the rate of hospitalisations per person year was 0.94 (95% CI 0.76 to 1.14) by month 24.⁵⁴ Updated data showed this rate to be 0.7 per person year after 36 months (no CI reported), with natural history range of hospitalisations for type 1 SMA reported as between 4.2 and 7.6 every year.²⁴⁰ At five years, hospitalisations were down to 0.55 per person year, while 22% of children had not required any hospitalisation since starting risdiplam treatment.⁵⁶

Type 2/3

No evidence was found for types 2 or 3 SMA.

13.4.2.4 Respiratory function

13.4.2.4.1 FVC

SLR evidence

No evidence was found for presymptomatic or type 1 SMA.

Types 2 and 3

One study⁴⁸, as reported in the earlier review, showed that there were no significant changes in the forced vital capacity (FVC) among the participants in the assessment of respiratory function over 24 months. Further evidence, from an earlier company submission,⁴⁴ at 60 months showed a non-significant decline in the mean change from baseline in FVC {18.5% (17.29%)}

Multiple types

The JEWELFISH study reported a mean change of 0.14% (95% CI –2.64 to 2.92, n = 113) from baseline to month 24 for the sniff nasal inspiratory pressure test.⁶²

13.4.2.4.2 Respiratory plethysmography

SLR evidence

No evidence was found for presymptomatic SMA.

Type 1

One study⁵⁴ reported results from the FIREFISH trial on the effects of risdiplam on respiratory plethysmography in type 1 SMA patients. Fourteen infants (34%) achieved a phase angle reduction of at least 30 degrees from baseline at 24-months follow-up.

No evidence was found for types 2 and 3 SMA.

13.4.2.5 Complications

Nothing reported.

13.4.2.6 Need for non-invasive or invasive ventilation

SLR evidence

Presymptomatic

Two records, one from the earlier review⁶⁸ and a newly identified record,⁵⁹ both from the RAINBOWFISH trial, reported on ventilation support. Results from both studies indicated that no patients required permanent ventilation, as all patients were alive without permanent ventilation at the clinical cut-off date.

Type 1

Data from FIREFISH, reported in the original review, indicated that, at month 12, 85% of infants remained permanent ventilation event-free (n=41).^{54,236} Although 70.7% of infants did not require any form of ventilatory support, a proportion of patients were still receiving ventilation support with 14.3% receiving bilevel positive airway pressure (BiPAP) for fewer than 16 hours per day and 19% receiving prophylactic ventilation. Additionally, 24% (10 infants) were receiving neither invasive nor non-invasive respiratory support. At month 24, the permanent ventilation event-free rate decreased to 83%, as one additional infant required permanent ventilation. The percentage requiring any form of ventilatory support remained unchanged at 70.7%, although 11 of 12 infants receiving pulmonary care were receiving prophylactic ventilation while the number of infants with neither invasive nor non-invasive respiratory support decreased to eight. Further evidence from the uncontrolled FIREFISH study²³⁶ reported in the earlier review showed that 19 of 21 infants enrolled had no need for permanent ventilatory support after 12 months.

No evidence was found for types 2 and 3 SMA.

Unreported type

One newly identified single arm study of newborns¹⁴⁸ evaluating infants who had positive newborn screening or prenatal testing for SMA and receiving risdiplam showed that all patients were without any ventilatory support at 8.5 months follow-up.

MAA evidence

Paediatric registry

The results for this outcome are taken from the updated April 2025 report.

Permanent ventilation was defined as any ventilation type for ≥ 16 hours/day continuously for > 21 days or tracheostomy. No patient was recorded as being on permanent ventilation, either at baseline or the most recent visit.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

No patients had events of permanent ventilation since commencing risdiplam treatment.

13.4.2.7 Stamina and fatigue

Nothing reported.

13.4.2.8 Mortality

SLR evidence

Presymptomatic

One study,⁵⁸ not reported in the earlier review, showed that all infants were alive at 12 months' follow-up.

Type 1

The FIREFISH study, including two reports from the earlier review^{54,236} and two newly identified reports,^{55,56} reported data on mortality among participants receiving risdiplam. One of the reports⁵⁴ from the earlier review showed that 38 of 41 (93%) infants were alive at 12 months, which remained unchanged at the 24 month follow-up. The other earlier study²³⁶ reported four deaths, including one in the interim and three deaths from SMA-related complications at 12 months. Further evidence from the newly identified report⁵⁵ showed that the percentage of patients who were alive decreased to 91% at 36 months. At 5 years, 91% of children were still alive and 81% were event-free (defined as alive with no permanent ventilation). Event-free survival was reported to be much better than natural history. Untreated infants from an alternative study had a median age for reaching death or permanent ventilation of 10.5 months (IQR 8.1 to 13.6), whereas this was inestimable at five years in FIREFISH due to a lack of events.⁵⁶

No evidence was found for types 2 and 3 SMA.

Unreported type

One newly identified study¹⁴⁸ of newborns who had positive newborn screening or prenatal testing for SMA and were receiving risdiplam stated that all patients were alive at 8.5 months follow-up.

MAA evidence

Paediatric registry

The results for this outcome are taken from the updated April 2025 report.

There were no additional deaths reported since the December 2023 report. One type 1 patient died before any follow-up visits due to a hypoxic head injury (primary) and SMA type 1 (secondary cause). One type 2/3 non-sitter died after 1 year follow-up from an unknown cause.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

Five patients died after commencing risdiplam. For three the primary cause of death was reported to be diseases of the respiratory system, one was due to spontaneous bacterial

peritonitis and one had an unknown cause. The patients were on treatment for a mean of 1.59 years (range: 0.95 to 2.75).

13.4.2.9 Adverse events

SLR evidence

Of note, the majority of adverse events (AEs) reported for this treatment also appear to be linked to the underlying condition or the method of administration, rather than to the treatment itself.

Presymptomatic

A newly included abstract (Servais 2024) reported data from the RAINBOWFISH clinical trial (NCT03779334).⁶⁰ According to EMA (2023), at the 12-month follow-up, 77.8% of participants experienced at least one AE, with a total of 81 events reported. The most frequently affected systems were the skin and subcutaneous tissue (38.9% of participants) and the gastrointestinal system (50.0%).⁶⁸ One Grade 3 AE, cystoid macular oedema, was observed but assessed as being unrelated to risdiplam treatment. No SAEs, deaths, or Grade 4 AEs were reported, and no Hy's law cases or liver-related abnormalities were identified. Seven of the 18 participants underwent Spectral-Domain Optical Coherence Tomography (SD-OCT) assessments for at least 12 months.⁶⁸ Two TEAEs, diarrhoea and skin discoloration, were reported in two participants, both graded as non-serious and Grade 1.⁶⁸ One event of skin discoloration was considered treatment-related by the investigator.⁶⁸ Additionally, one SAE of gastroenteritis due to norovirus was downgraded to non-serious following review. The overall AE rate in the study was 558.2 events per 100 patient years. A higher AE rate of 681.0 events per 100 patient years was observed in the first six months of treatment, decreasing to 401.1 events per 100 patient years in the subsequent 6 months.⁶⁸ There were isolated shifts in vital signs, including diastolic and systolic blood pressure, temperature and pulse rate, but these were not considered clinically significant. Retinal abnormalities, attributed to immaturity rather than treatment, were reported in one participant.⁶⁸

The findings reported in the Servais (2024) abstract were consistent with EMA (2023), confirming that no AEs led to withdrawal or treatment discontinuation.⁶⁸ Most AEs were mild and resolved over time. The safety profile in presymptomatic infants was comparable to that observed in older treated populations, with upper respiratory tract infections and diarrhoea among the most common events.⁶⁰

Type 1

Adverse event outcomes for symptomatic Type 1 SMA were drawn from the FIREFISH clinical trial (NCT02913482). Data from Masson et al (2022), cited in the earlier review, indicated that at the 24-month follow-up, 86 disease-related AEs were reported in 32 infants (78%), most of which were mild to moderate. Upper respiratory tract infection was the most common AE, reported in 54% of participants. The Canadian Agency for Drugs and Technologies in Health (CADTH) summary of FIREFISH Part 2 reported that all enrolled infants experienced at least one AE, with the most frequently reported being upper respiratory tract infection (46.3%), followed by pneumonia (39.0%), pyrexia (39.0%), and constipation (19.5%).⁵⁴

Day (2022) presented new data from the same study, reporting SAEs including pneumonia, respiratory tract infections, and acute respiratory failure. Upper respiratory tract infection remained the most common AE (55%), while pneumonia was the most frequently reported

SAE (34%), followed by respiratory distress (9%). In total, 68 SAEs were reported among 28 infants (68%). Post-hoc analyses highlighted 48 SAEs, with pneumonia affecting 13 infants, and bronchiolitis, hypotonia and respiratory failure each affecting two infants. According to CADTH data, 58.5% of infants (24/41) experienced SAEs, primarily respiratory-related. A further 24 SAEs were reported as of the data cut-off, with pneumonia and various forms of respiratory infection and distress occurring most frequently. AE rates per 100 patient years at 12, 24, and 36 months were 614.96, 432.14, and 216.21, respectively. Rates of pneumonia-specific AEs over the same timepoints were 34.37, 15.16, and 7.86 per 100 patient years. All 58 infants experienced at least one AE, with a total of 731 AEs reported. Six deaths (10%) occurred, with five infants (9%) experiencing at least one AE with a fatal outcome. Three infants (5%) experienced AEs that led to dose modification or interruption. Ten infants (17%) had TEAEs and 36 infants (62%) experienced Grade 3–5 AEs. No AEs led to treatment withdrawal. The most common AEs in more than 10 infants at 36 months were pyrexia (60%), upper respiratory tract infection (57%), pneumonia (43%) and constipation (26%). Serious AEs were reported in 74% of infants. Two infants (3%) experienced SAEs that led to dose modification or interruption and two (3%) had treatment-related SAEs. Pneumonia (36%) and respiratory distress (10%) were the most frequent SAEs, occurring in more than three infants.⁵⁵

Types 2 and 3

Safety data for patients with Type 2 or 3 SMA were primarily drawn from the SUNFISH trial (NCT02908685), which included a placebo-controlled phase followed by an open-label extension. Data from Mercuri et al (2022; 2023) and Oskoui et al (2023), all cited in the earlier review, were used to describe AE outcomes at both 12 and 24 months. In the risdiplam arm, 91.7% of patients experienced at least one AE between months 12 and 24.^{1,47,48,237} Between months 0 to 12, 20.0% of patients experienced at least one SAE and, during months 12 to 24, 20.8% reported at least one SAE. Among those initially in the placebo arm, 91.7% reported AEs while receiving placebo and 80.0% after switching to risdiplam. Grade 3–5 AEs occurred in 15.8% of patients in the risdiplam arm and 13.3% in the placebo arm between months 12 to 24.¹

Additional data extracted from Mercuri (2022 and 2023) for this review update showed consistent SAE rates in risdiplam-treated participants, ranging from 19.4 to 36.1 events per 100 patient year. Between months 0 to 12, 17.5% of participants in the risdiplam arm experienced Grade 3–5 AEs.^{73,237}

Safety data for patients with type 2 or 3 SMA were updated with new five-year follow-up findings from Servais (2025), reporting on the SUNFISH Parts 1 and 2 trials. The updated data indicated that the overall rates of AEs and SAEs per 100 patient years decreased over the five-year treatment period.⁵³ In SUNFISH Part 1, 98% of patients (50/51) experienced at least one AE and 26 SAEs were reported in total. The most common SAEs ($\geq 25\%$) were pyrexia (64.7%), vomiting (39.2%), cough (37.3%), upper respiratory tract infection (35.3%), nasopharyngitis (31.4%), COVID-19 (27.5%), gastroenteritis (27.5%) and oropharyngeal pain (25.5%).⁵³ In SUNFISH Part 2, 98.9% of patients (177/179) experienced at least one AE, and 173 SAEs were recorded in total. The most common SAEs ($\geq 25\%$) included upper respiratory tract infection (41.9%), nasopharyngitis (40.8%), pyrexia (34.1%), COVID-19 (33.0%), headache (26.3%), vomiting (25.7%), and diarrhoea (25.1%).⁵³ Pneumonia occurred in 9.8% of Part 1 and 10.6% of Part 2 participants. TEAEs were reported in 25.5% (13/51) of Part 1 participants and 20.7% (37/179) of Part 2 participants. Treatment-related SAEs occurred in two patients (1.1%) in Part 2 and none in Part 1. No participants discontinued due to TEAEs.

AEs led to dose modification in 15.7% of Part 1 and 17.9% of Part 2 participants.⁵³ Grade 3–5 AEs were observed in 21.6% of Part 1 and 38.0% of Part 2 patients. The total number of AEs was 1026 in Part 1 and 2800 in Part 2. TEAEs leading to modification or interruption occurred in one Part 1 patient (2.0%) and two Part 2 patients (1.1%).⁵³

Multiple types

Safety outcomes in previously treated patients with types 1, 2 and 3 SMA were assessed in the JEWELFISH trial (NCT03032172). Data from Chiriboga et al (2023; 2024) were cited in the earlier review, with additional findings extracted from the 2024 publication.^{61,62,68}

In Chiriboga et al (2023), the most commonly reported AEs were upper respiratory tract infection and pyrexia, each affecting 17% of participants (n=30). Pneumonia was the most frequently reported SAE, occurring in four participants (2%). The overall AE rate decreased from 648.0 events per 100 person-years during months 0–6 to 270.2 events per 100 person years during months 6–12. Similarly, the rate of SAEs declined from 33.9 events per 100 person years (95% CI 22.7–48.7) to 18.3 per 100 person years (95% CI 10.2–30.1). In total, 159 participants (92%) experienced at least one AE and 923 AEs were reported overall. Twenty-four participants (14%) experienced SAEs, one of which was treatment-related. Six participants had SAEs that led to dose modification or interruption, although none were attributed to risdiplam. One participant discontinued treatment due to an AE. A treatment-related SAE, supraventricular tachycardia, was reported in one patient previously treated with olesoxime and resolved without requiring modification to risdiplam.⁶¹

In Chiriboga et al (2024), the overall AE rate at 24 months was 323.40 events per 100 person years in participants with type 1 SMA (95% CI 263.69–392.58), and 335.63 events per 100 person years in those with types 2/3 (95% CI 317.11–354.95). The most frequently reported AEs were pyrexia (24%), upper respiratory tract infection (21%) and headache (18%). These findings suggest a favourable and stable safety profile of risdiplam in previously treated SMA populations.⁶²

13.4.2.10 *Health-related quality of life and Patient Reported Outcomes*

13.4.2.10.1 *EQ5DL (HRQoL)*

No SLR evidence was found reporting EQ5DL.

MAA evidence

Paediatric registry

This outcome was not reported in the April 2023 or December 2025 MAA report.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The adult registry highlighted the limitations of the PROMs evidence. Patient-reported data holds the risk of voluntary response bias and recall bias. PROMs data has been obtained from the registry and displayed in the report as a representation of a smaller proportion of the entire SMA population. Results must be interpreted with care.

Utilising a Pareto Classification of Health Change method, the registry reported whether a patient's health status was better, worse, the same or mixed (i.e. better on one dimension but

worse on another). Data was available for 45 non-sitters with a baseline and a follow-up submission. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] (for a breakdown over the follow-up period see Table 101).

For the EQ VAS the registry compared the first response of a patient to next response. The registry reported the number of patients who had an increase of ≥ 10 or ≥ 1 points, stayed the same, or ≤ 1 or ≤ 10 points. An increase in this metric is desirable as it equates to higher quality of life. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Table 101: Changes in EQ-5D-5L for patients using risdiplam treatment at each timepoint over the follow-up period

Risdiplam adult EQ-5D-5L		Time point (n/N)					
Measure	Type	6 months	1 year	1.5 years	2 years	2.5 years	3 years
Better	2/3 non-sitters	■	■	■	■	■	■
Same	2/3 non-sitters	■	■	■	■	■	■
Mixed	2/3 non-sitters	■	■	■	■	■	■
Worse	2/3 non-sitters	■	■	■	■	■	■
Better	2/3 sitters	■	■	■	■	■	■
Same	2/3 sitters	■	■	■	■	■	■
Mixed	2/3 sitters	■	■	■	■	■	■
Worse	2/3 sitters	■	■	■	■	■	■
Better	2/3 walkers	■	■	■	■	■	■
Same	2/3 walkers	■	■	■	■	■	■
Mixed	2/3 walkers	■	■	■	■	■	■
Worse	2/3 walkers	■	■	■	■	■	■

Abbreviations: NR = not reported as data was not available for this time point; n = number of patients who met the criteria for that category; N = overall number of patients

13.4.2.10.2 EQ5DY

No SLR evidence was found reporting EQ5DY.

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report. It is important to note that data reported here is from a pilot study aiming to recruit 50 paediatric patients. There was insufficient data to assess separate groups (i.e. SMA type). Additionally, the limited amount of data means the results require cautious interpretation.

Registry data was available for EQ5DY total score and VAS. The total score had six patients with available data at first entry and two were with a follow-up (latest available; see Table 102). No conclusions can be drawn from this data.

Table 102: Change in EQ5DY total score for those receiving risdiplam; from Paediatric MAA report December 2023

	Number of patients	Mean	SD	Median	Min	Max
First entry	6	11.5	2.3	11	9	15
Latest available	2	11.0	1.4	11	10	12
Change first to last available visit	2	0	1.4	0	-1	1
Abbreviations: MAA = Managed Access Agreement; SD = standard deviation						

The VAS was available for six patients at first entry. Two patients had a data point from with the latest available visit. No conclusions can be drawn from this data (see Table 103).

Table 103: Change in VAS for those receiving risdiplam; from Paediatric MAA report December 2023

	Number of patients	Mean	SD	Median	Min	Max
First entry	6	81.5	12.7	82.5	61	100
Latest available	2	74.5	23.3	74.5	58	91
Change first to last available visit	2	1.5	6.4	1.5	-3	6
Abbreviations: MAA = Managed Access Agreement; SD = standard deviation						

Adult registry

The adult registry did not report on this outcome in either report.

13.4.2.10.3 ITQoL-SF47

SLR evidence

No evidence was found for presymptomatic SMA.

Type 1

As reported in the earlier review, one FIREFISH record⁵⁴ examined the impact of risdiplam on HRQOL using the Infant and Toddler Quality of Life Questionnaire (ITQoL-SF47) at month 24. The results showed improvement in emotional health, temperament and mood, growth and development domains, with no change in bodily pain/discomfort, parent impact on time limitation, family cohesion, overall health domains, and a decline in physical abilities and general health perceptions.

No evidence was found for types 2 and 3 SMA.

13.4.2.10.4 INQoL

SLR evidence

No evidence was found for presymptomatic or type 1 SMA.

Types 2 and 3

Included in the earlier review, one study²⁴¹ examined the impact of risdiplam on quality of life using Individualized Neuromuscular Quality of Life questionnaire (INQoL), stating that all patients reported improvement in the quality of life the quality-of-life following treatment with risdiplam.

13.4.2.10.5 PGI-S

No SLR evidence was found reporting PGI-S.

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report. It is important to note that data reported here is from a pilot study aiming to recruit 50 paediatric patients. There was insufficient data to assess separate groups (i.e. SMA type). Additionally, the limited amount of data means the results require cautious interpretation.

There were six patients available at first entry and only two with data from a latest visit. For these two patients, one had no change in severity and one has an increase of 1 unit (higher scores are worse). No conclusions can be drawn from this.

Adult registry

The results for this outcome are taken from the original December 2023 report. The adult registry highlighted the limitations of the PROMs evidence: patient-reported nature holds risk of voluntary response bias and recall bias. PROMs data has been obtained from the registry and displayed in the report as a representation of a smaller proportion of the entire SMA population. Results must be interpreted with caution.

Data was available for 68 patients at first entry and 27 patients at a latest follow-up. Similar percentages between baseline and latest follow-up for moderate and severe levels were reported (26.47 to 22.22 and 72.06 to 74.07%, respectively). This suggests potential maintenance in the patient condition, though data is limited. Additionally, the means of the baseline (3.69 ± 0.55) and latest follow-up (3.70 ± 0.54) are similar. A sensitivity analysis was presented for those who had a PROM in ± 8 weeks visit window. This dataset had nine patients at latest follow-up, with 46 patients available at first entry. Moderate level rose slightly (30.34 to 33.33%), while severe levels decreased slightly (67.39 to 66.67%), representing probable maintenance in patient condition. Additionally, the means of the baseline (3.63 ± 0.60) and last follow-up (3.66 ± 0.50) are similar. Unlike the paediatric registry, the adult registry did not report if the patients available at last entry available showed improvement, maintenance or worsening.

13.4.2.10.6 PGI-I

No SLR evidence was found reporting PGI-I.

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report. It is important to note that data reported here is from a pilot study aiming to recruit 50 paediatric patients. There was insufficient data to assess separate groups (i.e. SMA type). Additionally, the limited amount of data means the results require cautious interpretation.

There were six patients available at first entry and only two with data from a latest visit. For these two patients, one had no change in severity and one had an increase of two units (higher scores are worse). No conclusions can be drawn from this.

Adult registry

The results for this outcome are taken from the original December 2023 report. The adult registry highlighted the limitations of the PROMs evidence: patient-reported data holds risk of voluntary response bias and recall bias. PROMs data has been obtained from the registry and displayed in the report as a representation of a smaller proportion of the entire SMA population. Results must be interpreted with care.

Data was available for 45 patients at latest follow-up, with 80 available at first entry. The proportion of patients reported for each level (from very much improved to very much worse) was similar at first entry and for those with the latest available data. This coincided with extremely similar means at baseline (4.02 ± 1.24) and last follow-up (4.02 ± 1.07), though these means showed a small decrease on average level. A sensitivity analysis was presented for those who had a PROM in ± 8 weeks of the visit window. This data set had 22 patients at last follow-up, with 59 patients available at first entry. Proportion of minimally improved showed an increase between the two data points, although so did minimally worse. Overall, it appears that the patients reported their condition to be slightly better, similar or slightly worse. Additionally, the means of the baseline (3.78 ± 1.21) and last follow-up (3.81 ± 1.13) are similar, with a slight increase. Unlike the paediatric registry, the adult registry did not report if the patients available at last entry available showed improvement, maintenance or worsening.

13.4.2.10.7 SMAIS

SLR evidence

No evidence was found for presymptomatic or type 1 SMA.

Types 2 and 3

Seven records^{44,47-49,53,55,237} reported data from the SUNFISH trial. Results from three records^{47,48,237} showed a numerical increase from baseline in SMAIS-ULM score in the risdiplam group compared to a decline in the placebo group at the 12-month follow-up, though this was not statistically significant (adjusted $P=0.39$). The results from two other records^{49,55} showed that patients and caregivers reported stabilisation or continuous improvements in the SMAIS-ULM total score change from baseline with risdiplam treatment over 36 months.

Newly identified outcome data from the SUNFISH trial in the initial submission⁴⁴ and another study⁵³ showed that the mean change from baseline in caregiver-reported SMAIS-ULM total score at 5 years was 2.65 whilst that of patient reported (>12 years old) was 0.94 (4.22) indicating that patient and caregivers reported continuous improvements in the change from baseline in SMAIS-ULM score over 5 years.

Multiple types

One record⁶² reporting data from the JEWELFISH trial showed an increase in the caregiver-reported SMAIS-ULM total score from baseline to month 24. At month 24, the mean change from baseline in caregiver-reported SMAIS-ULM total score was 1.90 (95% CI 0.70–3.10; $n=110$).

One newly identified study¹⁵⁰ investigating the effectiveness of risdiplam in type 1 and 2 SMA patients for 3 years using the SMAIS showed that most patients reported clinically meaningful improvement, except for two patients. The reported SMAIS scores showed a positive correlation to RULM scores at 12 months and 24 months. All three patients with zero RULM scores at baseline did not show improvement in motor function but had improvement in SMAIS, including drinking or using a keyboard.

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report. It is important to note that data reported here is from a pilot study aiming to recruit 50 paediatric patients. There was insufficient data to assess separate groups (i.e. SMA type). Additionally, the limited amount of data means the results require cautious interpretation.

Table 104 shows data at first entry to the patient registry whilst on risdiplam and for the most recent visit. In addition, a summary of changes from first to last available assessment is shown. Where individual items are missing, an adjustment has been made to the total score, so that the total is expressed out of the total number of items (similar to the approach for motor outcomes). Due to the limited data, no conclusions can be drawn.

Table 104: Change in SMAIS for those receiving risdiplam; from Paediatric MAA report December 2023

	Number of patients	Mean	SD	Median	Min	Max
First entry	5	22.4	5.0	22	17	30
Latest available	2	26.5	6.4	26.5	22	31
Change first to last available visit	2	3	2.8	3	1	5
Abbreviations: MAA = Managed Access Agreement; SD = standard deviation; SMAIS = Spinal Muscular Atrophy Independence Scale						

Adult registry

The results for this outcome are taken from the updated April 2025 report. The adult registry highlights the limitations of the PROMs evidence: patient reported nature holds risk of voluntary response bias and recall bias. PROMs data has been obtained from the registry and displayed in the report as a representation of a smaller proportion of the entire SMA population. Results must be interpreted with care.

The adult registry reported whether patients reported an increase, the same, or decrease in SMAIS-ULM. Data was available with for 42 non-sitters, with a baseline and a follow-up submission.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] (for a breakdown over the follow-up period

see

Table 105).

Table 105: Changes in SMAIS-ULM for risdiplam users at each timepoint over the follow-up period

Risdiplam adult SMAIS-ULM		Time point (n/N)					
Measure	Type	6 months	1 year	1.5 years	2 years	2.5 years	3 years
Increased	2/3 non-sitters	■	■	■	■	■	■
Same	2/3 non-sitters	■	■	■	■	■	■
Decreased	2/3 non-sitters	■	■	■	■	■	■
Increased	2/3 sitters	■	■	■	■	■	■
Same	2/3 sitters	■	■	■	■	■	■
Decreased	2/3 sitters	■	■	■	■	■	■
Increased	2/3 walkers	■	■	■	■	■	■
Same	2/3 walkers	■	■	■	■	■	■
Decreased	2/3 walkers	■	■	■	■	■	■

Abbreviations: SMAIS-ULM = Spinal Muscular Atrophy Independence Scale-Upper Limb Module; n = number of patients meeting this criterion; N = overall number of patients; NR = not reported as data was not available for this time point

13.4.2.10.8 EK-2

No SLR evidence was found reporting EK-2.

MAA evidence

Paediatric registry

The results for this outcome are taken from the updated April 2025 report.

The EK-2 scale assesses activity and participation in individual with non-ambulatory SMA. The scale covers eight daily-life categories including wheelchair use and transfers, trunk mobility, eating, swallowing, breathing, coughing and fatigue. A higher EK-2 score indicates a greater level of functional impairment.

No formal analysis was conducted and individual participant data was provided in graphical format. Most individuals maintained their level of function. Type 1 patients showed a trend towards improvement. However, some patient scores increased over time (i.e. worsened). It is important to note that this data was not mandated and has not been cleaned to the same degree as mandated items.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The adult registry conducted MMRMs for type 2/3 non-sitters and sitters. For sitters, the baseline includes 81 patients, with a decrease in EK-2 scores (positive impact) observed over the follow-up timepoints. At 2.5 years, 13 patients were included in the analysis, which is the last data point with enough patients to report a result. There are no statistically significant changes, but the numerical trend suggest improvement in the scores. For sitters, there were 85 patients at baseline and six at 2.5 years follow-up. No statistically significant changes are reported. Numerically, there is initial maintenance in the EK2 score, however, this is not maintained over the follow-up with small increases from 1.5 to 2.5 years, which suggests some degree of worsening. However, data is limited at the later timepoints.

13.4.2.11 *Other outcomes*

13.4.2.11.1 *Clinical Global Impression Scale (CGI-S)*

SLR evidence

No evidence was found for presymptomatic or type 1 SMA.

Types 2 and 3

One newly identified study¹⁴⁹ reported that "no patient showed worsening in CGI-S at 8 months."

13.4.3 Nusinersen, risdiplam and OA (comparative evidence)

No comparative evidence was found for nusinersen versus risdiplam for bulbar function, hospitalisation, respiratory function, complications, ventilation, or stamina and fatigue.

13.4.3.1 Motor function

No comparative evidence was found for nusinersen versus risdiplam for WHO motor milestones, CHOP-INTEND, HINE-2, BSID-III, RHS, or MFM.

13.4.3.1.1 RULM

SLR evidence

No evidence was found for type 1 SMA.

Types 2 and 3

The current review identified one study assessing the impact of both nusinersen (n=52) and risdiplam (n=73) treatment on type 2/3 patients.¹⁵⁷ This prospective, multicentre cohort study of children (aged 2-10 years) in Iran reported statistically significant improvements in RULM scores from baseline to follow-up (3 and 6 months) for both treatments. When comparing both treatments, no statistically significant differences were observed.

Two models were conducted to compare effectiveness between the drugs. In the first model, HMFSE and RULM score before medication therapy and medication type were included. In the second model, HFMSE and RULM scores before medication therapy, medication type, age at SMA diagnosis, age at start of treatment, sex, SMN2 copy number, scoliosis and use of an assistive device were included.¹⁵⁷

As previously stated in Section 11.6.2, making comparisons between the two treatments is difficult due to differences in population characteristics. This study further exemplifies this as, at baseline and after employing the eligibility criteria, there were statistically significant differences in the risdiplam and nusinersen groups for age at start of treatment (mean 92.2 ± 29.4 vs 80 ± 31.9 , respectively), sex (female = 51 vs 24, respectively), scoliosis (no = 30 vs 52, respectively), using an assistive device (no = 46 vs 51), HFMSE (mean 20.64 ± 17.56 vs 31.3 ± 17.86), and RULM (mean 17.75 ± 11.5 vs 26.18 ± 11.02). This shows clear differences, including supporting the previous narrative that those receiving risdiplam generally have a worse condition at baseline than those receiving nusinersen, as evidenced by the higher motor function scores for nusinersen patients.

It is also worth noting that, in the demographics table and the flow diagram of patient numbers, the numbers do not always equate to each other. For example, there were 46 people who did not use an assistive device for risdiplam and 49 who did (total = 95). The same demographic for those treated with nusinersen reported that 51 did not use a device and 18 did (total = 69). Both numbers are larger than the number of patients reported to be included in both groups at baseline (73 and 52, respectively). It is unclear why these discrepancies exist.

A positive of this research is that it is the first to compare the drugs directly in the same clinical setting. However, it was deemed implausible to randomise the groups due to the differences in eligibility for each drug.

13.4.3.1.2 HFMSE

The current review identified one study assessing the impact of both nusinersen (n=52) and risdiplam (n=73) treatment on type 2/3 patients.¹⁵⁷ This prospective, multicentre cohort study of children (aged 2-10 years) in Iran reported statistically significant improvements in HFMSE scores from baseline to follow-up (3 and 6 months) for both treatments. When comparing both treatments, no statistically significant differences were observed.

Two models were conducted to compare effectiveness between the drugs. In the first model, HMFSE and RULM score before medication therapy and medication type were included. In the second model, HFMSE and RULM scores before medication therapy, medication type, age at SMA diagnosis, age at start of treatment, sex, SMN2 copy number, scoliosis and use of an assistive device were included.¹⁵⁷ The caveats to this study regarding differences in treatment groups and reporting indifferences reported in the RULM section above also apply here.

13.4.3.1.3 Tool not reported

One newly identified, uncontrolled study¹⁵⁸ reported data for the effects of both nusinersen and OA on motor function in type 1 SMA patients, where the tool was not reported. Improvements/maintenance from baseline in motor milestones were observed in 5/10 patients treated with nusinersen monotherapy, in 8/8 patients treated with OA monotherapy and in 7/9 patients who switched from nusinersen to OA. The mean time to initial improvement in any motor milestone in months (mean, SE) were 7.3 ± 3.8 for (n=10) patients treated with nusinersen monotherapy, 1.5 ± 0.7 for (n=8) recipients of OA monotherapy and 3.9 ± 1.4 for (n=9) patients who switched from nusinersen to OA.

13.4.3.2 Mortality

SLR evidence

No evidence was found for presymptomatic or type 1 SMA.

Types 2 and 3

The current review identified one new study that reported mortality of patients receiving either risdiplam or nusinersen treatments.¹⁵⁷ Across both treatment groups, one death was reported, which occurred in the nusinersen group. The patient was type 2 and had a history of respiratory problems with decreased FVC and mild scoliosis. The patient developed a severe respiratory infection, leading to respiratory arrest.¹⁵⁷

13.4.3.3 Adverse events

SLR evidence

No evidence was found for presymptomatic or type 1 SMA.

Types 2 and 3

The current review identified one new study that reported AEs of patients receiving either risdiplam or nusinersen treatments.¹⁵⁷ Two patients had minor complications, with one patient experiencing abdominal cramps after risdiplam, which resolved spontaneously. The other patient had back pain and nausea after a nusinersen injection, which was managed with hydration and anti-nausea medication in subsequent injections.¹⁵⁷

13.4.3.4 Health related quality of life

SLR evidence

No evidence was found by individual SMA type.

Multiple types

The original review identified one study reporting HRQoL following nusinersen, risdiplam or OA treatment.⁹ The study was a prospective cohort study including patients with type 1 (n=7), type 2 (n=9) and type 3 (n=11) SMA. The PedsQL was utilised and the sub scales of school functioning, emotional functioning, social functioning and physical functioning were presented along with the total score.

While the results are not reported separately by drug type, meaning comparisons are not possible, the impact of the disease modifying therapies overall is considered here. The results show that 15 patients had an improved quality of life, while the other patients had the same or a lower level of quality of life at follow-up (18 months). SMA type 3 appeared to maintain their level of quality of life, with minimal changes in scores across all domain and total score. Those with type 1 appeared to have less consistent quality of life ratings, with decreases for school (-5.56 points), social (-2.38 points), physical (-2.08 points) and total scores (-2.03 points). However, emotional functioning scores did show some improvement (2.38 points). Finally, those with type 2 SMA appeared to have the most consistent increases in quality of life, showing improvements for each sub scale and total score; point score increases ranged from 1.85 for school functioning to 6.02 for physical functioning.⁹

13.4.3.5 Bulbar function

Type 1 SMA

One newly identified¹⁵⁸ reported evidence for the effects of nusinersen compared to OA on cry function, swallowing function and eating function in type 1 SMA patients. The proportions of patients showing maintenance or improvements in cry function were 5/10 for those who received nusinersen monotherapy, 8/8 for people who received OA monotherapy and 6/9 for those who switched from nusinersen to OA. Maintained or improved speech function was observed in 7/8 patients who received nusinersen monotherapy, 6/6 who received OA monotherapy and 6/8 who switched from nusinersen to OA. Eating function was maintained or improved in 4/8 patients who received nusinersen monotherapy, 5/6 who received OA monotherapy and 5/9 who switched from nusinersen to OA.

13.5 Qualitative analyses

The following section presents results from the qualitative framework analyses described in Section 9. Qualitative analyses relating to economics is presented in Section 15.3.

13.5.1 Ability to socialise

People living with SMA and their carers expressed that the impact of the condition left them feeling isolated and less able to socialise with other people. Some people who lived with SMA described that they struggled to find other people to speak to. Others noted that that they would isolate themselves because they had lost physical functions, such as being able to feed themselves. In turn, this contributed to anxiety surrounding socialising with other people. The impact of poor bulbar function on the ability to communicate was also highlighted by one parent of a child with SMA. Furthermore, people with SMA can feel their ability to interact with others is impacted by their need to self-isolate. People mentioned that lockdown made them feel isolated, though others spoke more generally about self-protecting.

“Desperately looking to be an active member of society as I have always been for myself and my family, I Have developed a hermit personality as you are self protecting which is not living.”
– Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with Type 4 SMA

[REDACTED]

Carers of those with SMA also suggested that their social lives were diminished, either due to their caring responsibilities or because of a lack of support and not being able to ask others to take on their caring roles. This not only impacted friendships but also familial and intimate relationships. Carers and parents of people with SMA often cited that the nature of their relationships with partners and spouses had changed or even ended as a result of the caring responsibilities required. They expressed that they could not spend quality time together to maintain their relationships.

“Marriage of 25 years ended because caring for a child/young person/adult has a massive impact on relationships. Making sure a younger sibling is able to enjoy life too creates a huge strain and leaves you juggling many balls in the air.” – Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; carer of a child with SMA

“It has changed the marriage between my husband and I to the point where we exist as carers only. We work together to care for our children but are separate at night due to one of us on night shift in another room. We are handling daily stress and sadness about our child and it makes us argue/ feel frustrated with each other.” – Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; carer of a child with SMA

Both people with SMA and carers of those with SMA noted that treatment had a positive impact on their social lives. One adult noted that this was because their condition had stabilised as a result of treatment with nusinersen.

“But what Spinraza does, it helps to stabilise the condition and I’ve noticed that stabilisation in my condition. That has enabled me to hold a bit of hope for the future, hope that I will be able to live a full life, go on lots of holidays and continue to work, continue my social life and my hobbies and activities.” – Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with Type 3 SMA

[REDACTED]

Carers for children with SMA noted the positive impacts of treatments on both themselves and their children. They noted that their children were able to play with friends and that, because the need to avoid infection had reduced, they and their families also socialised more. One carer suggested that if their child was not receiving any treatment, the fear and anxiety they would feel would have a negative impact on their own social life.

13.5.2 Activities of daily living

Activities of daily living were often impacted by the symptoms and complications associated with SMA, such as reduced bulbar and respiratory function, as well as motor function.

[REDACTED]

People talked about not being able to undertake activities independently. Carers in particular noted that they needed to help the people they were looking after to eat, drink, dress, go to the toilet and wash themselves. The impact of poor bulbar muscle function on being able to eat safely without choking was often a concern. Furthermore, the amount of assistance needed with regards activities of daily living could be substantial.

“His physical needs consisted of dressing, toileting, bathing, washing, assisting with meals and snacks throughout the day, getting [my child] 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 hours a day.” – Patient expert submission 2 (carer for child with SMA)

[REDACTED]

There was also a financial impact on people with SMA, their families and carers on facilitating activities of daily living, due to the need for adaptations and equipment. These included wheelchairs to help with mobility, but also adaptive beds, hoists, adapted toilets, transfers and standing frames. Some people also talked about the need to adapt their vehicles or to have wheelchair-accessible vehicles to enable them to travel beyond their own homes.

The impact of treatment on activities of daily living were highlighted by people with SMA and their carers. Adults with SMA noted that they could enjoy their life more following treatment. Being able to eat and drink independently was a common theme, which was particularly highlighted by carers and patient experts. Adults taking either nusinersen or risdiplam noted that the treatments allowed them to cut up and eat more than soft foods as the fear of choking had been reduced.

[REDACTED]

A case study from one adult with type 3 SMA noted that only needing to have nusinersen administered every four months was convenient, as they were able to forget about the need for medication and continue with their life in-between doses. A patient expert (submission 2, carer for a child) noted that taking risdiplam did not impact on their daily lives and so their child's needs could be more easily met.

13.5.3 Adverse events

Experiences of adverse events from nusinersen, risdiplam and OA were described by some people with SMA, as well as some carers for those with SMA. Some reflected on anecdotal evidence that adults using nusinersen have experienced headaches and fatigue, with gastrointestinal side-effects reported in adults taking risdiplam. One professional expert noted that, although rare, some patients discontinue risdiplam due to the side-effects. One patient organisation submission noted the potential for serious side-effects for those undertaking OA if they had an underlying infection, as this could lead to a systemic immune response. This possibility often led to families shielding themselves from infection for either all or part of the three-month monitoring phase post-administration. One professional submission noted that side-effects linked to treatment could potentially be a reason for discontinuing or switching treatments.

However, people with SMA and their carers often noted that they did not experience adverse events due to treatment either with nusinersen or risdiplam.

"We are usually in and out of the hospital within about 4 hours with no side-effects." – Patient expert submission 3 (carer for a child with SMA)

"[My child] has never had any side effects from this treatment." – Patient expert submission 2 (carer for a child with SMA)

[REDACTED]

Although nusinersen requires administration through a lumbar puncture, some also suggested that they found the procedure to be acceptable and were willing to accept minor side-effects of the treatment. However, one person noted that they particularly disliked the process of a lumbar puncture.

"Looking back, I would not have changed my decision to get Spinraza, I find the lumbar punctures completely fine, a couple of minor side effects but they are not really noticeable" – Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with Type 3 SMA using nusinersen

[REDACTED]

13.5.4 Bulbar function

The negative impact on the lives of people with SMA due to weakened bulbar function was a common theme across submissions and case studies. As previously noted, bulbar function is inherently connected to both the ability to eat and drink independently and safely, but also to be able to communicate and socialise with others. Several of the submissions and case studies highlighted the difficulties associated with the loss of bulbar function, including not being able to chew or swallow, needing to modify diets to ensure safety, and the potential for tube feeding. The potential for aspiration was also highlighted. One parent noted that their child's weakening ability to swallow meant that they had been aspirating, while another had been told to start thickening powder.

Submissions often spoke of the positive impacts of treatment on bulbar function, both in terms of their ability to communicate and to swallow.

“I can now talk to people and they understand every word because my voice box works again.”
– Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with SMA

“My swallow ability is stable and it is very important for me too. Because it is in a rather poor condition and if it progresses, I could lose the ability to eat tough food.” – Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with SMA

However, one adult with SMA noted that they had experienced little improvement in bulbar function from treatment, other than less aspiration.

Some people spoke about the specific effects of risdiplam on bulbar function. One adult noted that they no longer had to worry about choking, one parent noted their child had regained their swallowing function, while another carer highlighted how their child had improved from being completely tube fed to mostly eating orally since taking the medication.

[REDACTED]

Despite these improvements, many of the submissions and the EAG’s discussions with PPI and professional groups highlighted that data surrounding the impact of treatment on bulbar function is currently lacking. In discussion with the EAG, some members of patient groups noted that the monitoring of bulbar function in children is not always extensive. One submission noted that although the tests are used to measure bulbar function in response to treatment within clinical settings, these often show as non-significant despite the patient and carer perception that their function and quality of life have improved. One carer told the EAG that their child had no further clinical follow-up or tests regarding bulbar function after one video fluoroscopy and they were reliant on their own perception to know whether their child’s function had stabilised or improved. Professionals noted in discussion with the EAG that it has only been more recently that clinical trials have begun capturing the impacts of treatment on bulbar function in people with SMA, leading to gaps within the current evidence.

13.5.5 Complications of SMA

There was some brief discussion on complications associated with SMA within the submissions and case studies, particularly surrounding scoliosis and contractures. One parent in a patient expert submission (submission 3) noted that their child’s contractures restricted their overall mobility in their knees, ankles, hips and shoulders, highlighting the interconnected nature of complications and physical function in those with SMA. Scoliosis was noted by one submission to be a common occurrence in people with SMA, which impacted on mobility but also had the potential to compress the internal organs and cause the person pain.

[REDACTED]

[REDACTED]

13.5.6 Equality considerations

As previously noted, the submissions highlighted geographical inequalities in care and provision of equipment across the UK. Beyond these service and resource use factors, the submissions also highlighted delays in access to treatment and the impact that these waiting times had on the condition. This included difficulties in accessing treatment through the current MAA.

“Took a long time to be offered MAA. I think because there weren’t many people of my age and the hospital wanted to offer the drug simultaneously to a meaningful sample.” – Quotation from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult (SMA type and treatment unknown)

“And then it was YEARS before I could get my hands on the drug, my hands started to go, I couldn’t drive my car any more, I couldn’t even drive my chair reliably any more.” – Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult (SMA type and treatment unknown)

[REDACTED]

The lack of availability of treatment and care for adults compared with children with SMA was also highlighted within the submissions. One professional expert submission highlighted the differences in access to treatment and care between adults and children with SMA.

“There is a notable difference in the access of adults to standard of care compared to children. In a recent patient survey, a 59% difference for access to physiotherapy (100% in paediatric, 41% in adults) was observed between adult and paediatric populations. Similar patterns were seen with access to interventions, including a 46% difference for access to supported standing (53% paediatric, 7% adult) and 45% difference for access to splints (59% paediatric, 14% adult).” – Association of British Neurologists submission

Adults with Type 4 SMA currently do not have access to treatment via the MAA. In discussion with the EAG, patient groups noted that treatments are still as valuable for adults than presymptomatic patients, with one patient expert noting that a lack of access to treatment options means that people with Type 4 SMA can be left unable to work and increasingly reliant on their families and friends to care for them.

As this issue highlights, the difficulty adults had in accessing treatment was often connected to the strict eligibility criteria linked with treatments. The limited eligibility criteria for OA was highlighted within submissions, noting that most of the SMA population within the UK are ineligible for the gene therapy. One patient organisation submission also noted that access to OA was further limited by geographic location, as there are currently only seven infusion centres in the UK. Furthermore, others highlighted that the difficulty of administering nusinersen to those who had spinal fusions means it may not be a viable option for adults with SMA.

The issues surrounding eligibility for the different treatments emphasised the need for a range of treatments to be available to the SMA community to meet different needs. Expert submissions and patient organisations emphasised that both nusinersen and risdiplam needed to be accessible to ensure that all people with SMA could have access to treatment.

“Both should be available as some patients cannot tolerate or access one (for example after spinal fusion). Operating on the principle that those who are long term ventilated unnecessarily have a less good quality of life is an equality issue.” – Professional expert submission

“Patients have seen benefits from treatment across the severity spectrum. Access for all from those fully ventilated to those living with type 4 is the only way to ensure equity of access for the whole SMA community.” – SMA UK/ MD UK/ Treat SMA joint organisation submission

13.5.7 Hospitalisations

The need to be hospitalised or to visit A&E within the submissions was often due to declining respiratory function. Two patient expert submissions noted that their children had been hospitalised because of respiratory issues that, in one example, also led to the need for further intervention and ventilation.

"I also had to watch his respiratory system decline which resulted in multiple hospital admissions" – Patient expert submission 2 (carer for child with SMA)

"Unfortunately, the remainder of 2017 saw three further long PICU admissions throughout which we were trained how to use a bi-pap ventilator, a cough assist machine and how to administer aggressive respiratory physiotherapy and invasive deep suction." – Patient expert submission 3 (carer for child with SMA)

Another submission highlighted good respiratory health as being a major factor in preventing people with SMA from being hospitalised. Undertaking treatment was stated to have improved respiratory function, which subsequently reduced or eliminated the need to be hospitalised. This was highlighted by patients, carers and professional experts.

"I'm so much stronger and haven't had a hospital admission for a common cold in 4 years" - Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; adult (SMA type and treatment unknown)

“Since [my child] has been on risdiplam, he has not had a hospital admission” – Patient expert submission 2 (carer for child with SMA)

[REDACTED]

13.5.8 Impact on education and ability to work

The physical symptoms and complications of SMA, as well as the need to care for people with SMA and assist them with daily activities, was noted to have a profound effect on the ability to attend school and go to work.

"I was diagnosed approx 5 years ago where I had to leave a job I loved for 25 years as manager of local Airport for Loganair as I couldn't do the hours due to extreme fatigue and experience anxiety which was very new to me being a very calculated person before SMA." – Case study from SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with Type 4 SMA

[REDACTED]

Parents and carers for children with SMA stated that they often did not feel supported by the education system. They spoke about how the physical impact of SMA hindered access to mainstream education. Some people in the submissions appeared frustrated by the lack of physical accessibility within nurseries and schools, particularly as SMA does not affect children's intellect.

"We have faced issues with [child's] nursery & him not being able to be with his peer group due to the class being upstairs and health and safety issues with no 121 support being offered by the council, so he has to stay in the baby class until we can get him into pre-school. This is detrimental to his cognitive and communicational skills as SMA does not affect his intelligence, he has struggled seeing his peers move up to the next class." – Case study from SMA UK/ MD UK/ Treat SMA joint organisation submission appendix; carer for child with Type 2 SMA

It was not only people with SMA whose education and working lives were affected by the condition but also that of their families and carers. Carers for children noted the significant impact on siblings' education, including absences due to the need to shield and compounded anxiety during already stressful periods, such as during exams.

"[...] She also had to try the steroids on drip for 3 days, but we knew this could be a side effect from Zolgensma, it can be hard with having other children who still need to go school I feel like it's pretty hard going on them" – Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; carer for child with SMA

"My eldest daughters went through GCSE's and A-levels, revising at [my child's] bedside, managing the trauma of his condition and the impact on their daily lives, alongside exam stress." – Patient expert submission 3 (carer for child with SMA)

The working lives of parents and carers for those with SMA were also impacted. Some feared they would need to give up their jobs while others felt as if they were forced to leave their jobs to take on caring responsibilities. As previously described, this places a substantial financial strain on families.

"We had no idea if we could keep working, if we would lose our house and how were we going to cope watching our son deteriorate before our eyes." – Case study from SMA UK/ MD UK/ Treat SMA joint organisation submission appendix; carer for child with Type 2 SMA

“When my son was diagnosed with SMA Type 1 at 3 months old, I had no choice but to give up my job” – Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; carer of a child with Type 1 SMA

“Electric, fuel for the van, insurance, food, extra hotel room for carer when we go away overnight impact us massively. I can't work apart from 10 hours per week I get paid as part of my son's care team as I'm always on call/ home alone with him.” - Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; carer for adult with SMA

The benefits of treatment both on education and ability to work were highlighted throughout the submissions. Some noted that the children they looked after were able to attend school more regularly, which also had an impact on their siblings' ability to attend. The stabilisation of the condition that receiving treatment provided for people was noted to increase the likelihood that they could keep working into the future. Some described this as one aspect of being able to live a normal and productive life.

“[...] now she is consistently attending school things have improved significantly.” – Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission appendix; carer for a child with SMA

[REDACTED]

“This is making my working day so much easier! I used to want to cry in pain from a day at work, typing on laptop - not anymore. I no longer feel that 'withdrawing from work' is on the horizon and I can earn a good income for at least another 10-15 years provided the [treatment] benefits are maintained” – Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission appendix; adult with Type 2 SMA

However, measuring the impact of SMA and treatment on education was highlighted as problematic. In discussion with the EAG, one patient group representative queried whether the differences treatment makes to school attendance and attainment could be more regularly monitored and quantified.

“Say there's no data, which I agree, there isn't any that I know of, is there any way in terms of education getting any data with attendance prior to treatment and after treatment, is there anything that can be done that way? Because I know for example, was 30% attendance, he's now 96.” – Patient group representative in discussion with the EAG

Furthermore, patient representatives in discussion with the EAG also highlighted the financial impact on families and carers as being an important issue, suggesting that the economic model should include carer costs and the impact on the wider family as well.

“I was just quite pleased to see that the carers bit was in there as well. And I think we just got to be how that, how that is actually calculated within the cost modelling side of things because, like I said before, that kind of ripple effect, the carer, is quite wide and it could be the impact on siblings, parents, aunties, uncles, grandparents, and it gets bigger and bigger. School, you know. Everything else in between that. So I think it's just how that is calculated as a number you know, is quite key actually.” - Patient group representative in discussion with the EAG

13.5.9 Independence

Independence was a cross-cutting theme across the submissions, as it was often mentioned alongside the ability to do activities of daily living, the need for support from family, friends and carers, and the need for assistive devices and adaptations. The overall importance of independence and how encompassing it is for those living with SMA and those who care from them was summarised in a discussion between the EAG and PPI groups.

“I mean in terms of independence, independence to communicate, independence to usual wheelchair, independence enables you to type on a keyboard, independently to work, like independence is huge. I mean, that links into mental health that links things to impacts and siblings, on to carers, on to going into school on education. I mean, but that's huge. Independence is massive” – Patient group representative in second discussion with the EAG

[REDACTED]

An organisation submission noted that not allowing continued access to treatments would mean their level of dependence on others would increase. Indeed, when discussing independence directly, many people with SMA and their carers noted the specific impacts of treatment on how they could function without help from others.

[REDACTED]

13.5.10 Looking to the future

Two clear sub-themes emerged, surrounding anticipatory grief and feeling greater hope for the future. Firstly, the concept of anticipatory grief was captured in experiences related to the life of an SMA patient and what it is like to live with a progressive condition. Anticipatory grief captured not only mourning premature mortality but also living in a state of ongoing anxiety and fear about what functional losses may occur next as the condition progresses. This could be a loss or decline in mobility, swallowing function, energy, independence, or multiple aspects simultaneously. One expert patient submission from an adult with SMA likened this experience to living with “chronic sorrow”.

“SMA Being a progressive condition always means that individuals are often faced with the knowledge that you are soon to lose another everyday function, but without any indication as to when. For example, I may be able to clean their teeth myself today but I know at some point in the future this will be impossible. I often refer to this as having 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. It is often said that someone who is in an accident, and perhaps loses the ability to walk, there is a grieving process for the loss of that function. This can take months if not years to recover from. 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.” - Patient expert submission 1 (adult with SMA)

Anxiety over the progression of the disease and potential functional decline was also reported within case studies, both from patients and carers for those of SMA. “SMA is an evil condition, one that condemns you to lifelong grief and sadness due to your constant decline” – Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult taking risdiplam (SMA type unknown)

“Living with a child with SMA is emotionally draining, I have recently contacted the doctor for counselling and treatment for stress and anxiety. It is a constant worry about the future and his independence.” - Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; carer for a child with Type 2 SMA (treatment unknown)

However, the data also captured the experiences of people’s lives following treatment and the impact this had on their outlook for the future. Receiving treatment with either nusinersen or risdiplam allowed patients and families to feel reassured. They often described the pronounced differences in their outlook on the future due to receiving treatment, and how they were able to plan their lives and futures.

“There is hope and there is evidence via the assessments that I am not deteriorating” – Quotation from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with SMA Type 2 being treated with nusinersen

[REDACTED]

“Rather than continued deterioration, Risdiplam has given me a future.” - Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult taking risdiplam (SMA type unknown)

“I can plan for my future, thinking about the next 5 or 10 years without wondering if I'll be significantly weaker by then. I'm able to make decisions about my life based on how I feel now, instead of how I'll feel if things get worse.” – Quotation from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with Type 2 SMA (treatment unknown)

This hopefulness about the future due to treatment was not just felt by patients themselves but also by carers. Both people with SMA and their carers described how the psychological burden had been relieved on their wider families.

“It was hope for my wife, was hope for my children, hope for my friends and other relatives who, in some regard, all expected me to die” - Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult taking risdiplam (SMA type unknown)

“[Patient] has been on treatment for 4 years, it's changed all our lives and lessened the burden on our mental health and anxiety for the future.” – Quotation from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; carer for child with Type 2 SMA, treatment unknown

13.5.11 Maintenance or stabilisation of condition

Across patient, carer, and professional perspectives, there was a strong suggestion across submissions that stabilisation and maintenance of motor function, respiratory function, bulbar function, stamina, and fatigue are meaningful outcomes in the context of SMA. The Association of British Neurologists noted that, in the context of the natural history of decline for those with SMA, no change in condition is an “excellent outcome.” The ability to preserve current abilities such as controlling a powerchair or swallowing can have a profound impact on quality of life. It was suggested that maintenance and stabilisation of the condition can support greater independence, functional ability and relationships.

“It’s acknowledged that the majority of those on this particular treatment are likely to be of the older population and therefore the perceived efficacy may be somewhat less, but I can tell you from personal experience, that is far from the truth. This deliver stability and that is what we should be looking to deliver with regards to treatment. Yes improvements are a bonus, but stability maintains lives, livelihoods, relationships and everything else.” – Patient expert submission 1 (adult with SMA)

“However, the value to an older individual 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.” - Patient expert submission 3 (carer for a child with SMA)

“young people or young adults are becoming stronger or maintaining their SMA, they’re able to go on to further education or go into mainstream education.” - Representative for a PPI group in discussion with the EAG

Maintenance or stabilisation in condition is also interlinked with emotional and psychological wellbeing (see Section 13.5.16). From the qualitative analysis, people who reported experiencing stabilisation of their condition also suggested a positive improvement in their psychological wellbeing, including reduced anxiety about the future, decreased fear of deterioration and less concern about mortality.

“It’s been a real mental soother to know I’m not getting weaker in theory and my results prove it.” – Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; person with Type 2 SMA aged between 15-20 years old

“There is hope and there is evidence via the assessments that I am not deteriorating.” – Quotation from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with SMA Type 2 being treated with nusinersen

The importance of stabilisation was also suggested to be particularly significant for symptomatic adults. Stabilising the condition can help prevent the need for costly and invasive interventions over time, such as increased respiratory support or nutritional measures like gastrostomy. The joint submission by SMA UK, MD UK and Treat SMA noted that the value of stabilisation for adults with the condition “cannot be underestimated,” while the Association of British Neurologists noted that stability in motor function as an adult in particular would mean people could continue to work and not need respiratory support or gastrostomy.

[REDACTED]

13.5.12 Mortality

Reduced mortality is a potential reality for many people living with SMA. The submission by the Association of British Neurologists highlighted how, without treatment, the life expectancy of someone with Type 2 SMA is between 30 and 50 years. In discussion with the EAG, a representative for a patient organisation noted most children with Type 1 SMA would die before the age of two.

Findings were closely linked with looking to the future, with adults describing their experiences of living with the knowledge of early mortality and how this impacted them throughout their life course.

“You need to understand little bit about what life growing up with SMA is like, when you are young you are told you will die in your teens... maybe... if you're lucky (or you were told this in my day), then you get through those years and you're told you might get to 30 odd... Then you get to that age and you start thinking "when am I going to die" - Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult taking risdiplam (SMA type unknown)

“I was told I would not live beyond the age of five, then in my 20s I was told probably not beyond 40, all of these have had massive impacts on my life constantly being concerned about getting close to dying.” – Patient expert submission 1 (adult with SMA)

Carers also shared their reflections on the impact of being told they would likely lose a child or loved one due to SMA.

“We were told the devastating news that he would not make it to his second birthday.” - Patient expert submission 3 (carer for a child with SMA)

The impact of access to treatment on patients' lifespan was noted across the submissions. The submission by SMA Reach UK noted that DMTs could reduce mortality, particularly for those with Type 1 SMA, while the Association of British Neurologists noted that the stabilisation in functions (particularly respiratory function) associated with nusinersen and risdiplam treatment would lead to increased life expectancy. Adult SMA Reach also anticipated that life expectancy would increase due to the impacts of treatment on respiratory function, motor function and other outcomes.

Additionally, adults reported that access to treatment has resulted in the stabilisation of the condition, which has meant they have less fear of dying when participating in aspects of life that some may consider routine daily events, such as getting a cold or flu or eating food. Adults with SMA reported feeling less fear of impending or early death because of the stabilisation in their condition.

“I'm not quite sure how to put this. Risdiplam has improved every part of my life. I can now talk to people and they understand every word because my voice box works again. I no longer feel like I'm dying. At all. Let alone soon.” - Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with SMA

“Treatment has now given me hope that while I may not live to 100, there is now no predefined expiry date that I am living to.” - Patient expert submission 1 (adult with SMA)

Carers also reported that their fear surrounding the reduced life expectancy of the people they were looking after had been alleviated due to the impact of treatments.

“Since [patient] 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.”
– Patient expert submission 2 (carer for child with SMA)

“If he had not finished those loading doses I’m certain he wouldn’t be here with us.” - Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; carer for a child with an unknown type of SMA who had been administered nusinersen and OA

13.5.13 Motor function

The impact of SMA on motor function was a common theme throughout the qualitative analyses but, from discussions with the EAG and within expert submissions to NICE, there was also an emerging focus on the way in which motor function as an outcome is measured and how this may not reflect the experience of those with SMA, that of their carers, or experiences of treatment. It was noted that, historically, efficacy measures have primarily focused on improvements in motor function and motor milestones. However, the qualitative analysis suggested that, with the availability of disease-modifying treatments and subsequent shift in the natural history, the patient and clinical community believe these measures do not fully capture all aspects of meaningful change for individuals living with SMA. In discussion with the EAG, clinicians highlighted the range of different measurement tools for motor function and their applicability to either adults or children, and to different SMA types. One clinician noted that a measurement tool such as the RHS or HMFSE may be useful for sitters or walkers, but another tool would need to be used for those with more advanced progression or severity. Furthermore, representatives of patient organisations told the EAG that the current tools used to measure motor function do not capture what they considered to be meaningful milestones.

“the motor milestones. I don’t think they’re anywhere near sensitive enough to capture the benefits. I think the first motor milestone that my son achieved that was the biggest celebration was being able to hold his head up by himself, when in a supportive chair to just being able to do that was huge and a massive impact on his quality of life. Being able to hold his head up and look around. And then the whole sitting thing. You have sitting, but then you have supported sitting. Like, my son can sit in a brace, a spinal brace for, for quite a long time. Time the brace off, he can still do it, but he’ll have to prop himself. It’s like, there’s sitting and there’s supported sitting and there’s sitting with your head up” – Representative for a PPI group in discussion with the EAG

“And I think it’s really important from a patient organisation’s perspective that the weighting is really heavy on the stories and the kind of, like I said before, the little moments, those, those things that really make a difference. Lifting a head up is very important. Or, you know, if somebody’s using an electric wheelchair rather than a carer putting their hands on to the device, they can do that themselves. That’s a tiny, tiny, tiny difference. But in terms of independence and quality of life, it’s an absolutely massive outcome.” - Representative for a PPI group in discussion with the EAG

A key finding from the qualitative analysis, which aligns with clinical and patient perspectives on meaningful treatment outcomes, is the value of stabilising, maintaining and slowing the decline in motor function. The Association of British Neurologists noted that both nusinersen and risdiplam were “likely to be effective” in stabilising motor function in adults with SMA,

subsequently also improving quality of life and participation. In their submission to NICE, a clinical expert also noted that, for symptomatic patients with SMA, slowing or stopping disease progression would be considered a clinically significant treatment response. The importance of stabilisation of motor function, as opposed to larger improvements in motor milestones, was also consistently described as an important treatment outcome by people with SMA and their carers.

I think that stabilisation is really the hidden benefit of this medication. Its not about helping me to walk again like I used to in my teenage years, but actually that stabilisation is so valuable to me as it keeps me independent which is actually such a full part of my identity and who I am.” – Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with Type 3 SMA taking nusinersen

”I have maintained my strength and improved in some aspects. For example, putting on my headset is very important to me and I no longer strain as much as I did.” - Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; teenager with SMA

“And then just to kind of clarify that for example, if we see that the patient is stable. For example, if we look at WHO motor function, if they remain as a sitter, that is a very good outcome for adult patients. So we also will try to emphasise that that it is a good outcome for adult patients to be remain stable. So we're not necessarily looking at gaining” - Professional group representative in discussion with the EAG

Further discussion surrounding maintenance and stabilisation of the condition can be found in Section 13.5.11.

An important emergent sub-theme closely linked to the preservation or stabilisation of motor function is the role of the fine motor skills. People with SMA discussed how smaller movements are crucial for enabling individuals to maintain independence, remain in their careers, attend school and participate in everyday activities. This includes vital tasks and activities of daily living, such as eating, drinking, operating electric wheelchairs, and using electronic devices without assistance.

“This means I am able to continue with my career with very limited functional use, for example, the ability to use a mouse with one hand. I no longer have the ability to type, I use voice recognition, but the ability to manipulate a computer easily using a mouse sustains my role. Yes, something as simple as that, these are the details that people do not understand.” - Patient expert submission 1

“I am now able to lift my hand from my lap to the control of my wheelchair without help” - Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with SMA

A submission from a clinical expert also noted that preserving fine motor function is especially important for individuals with SMA who are long-term ventilated, a group whose specific needs may not be fully addressed under the current MAA regulation.

Motor function is also closely tied to the experiences of carers, influencing their daily lives and having a psychological impact. It was suggested in the qualitative analysis that a person's ability to maintain as much independence as possible not only enhances their own quality of life but also greatly benefits their carers and wider families. Many carers described the emotional relief and improved wellbeing that comes from knowing treatment can help preserve their child's abilities and slow further decline. This sense of stability also allows carers the

space and capacity to support other children and family members, helping to restore some balance to family life.

“His physical abilities have got stronger in some areas and have maintained in the rest. I feel this is due to the medicine itself and as he is well the majority of time, he is able to participate in physical activities and physio. This improved strength has allowed me to be needed less and therefore I have more quality time with my daughter. Knowing your child’s condition will not deteriorate, is a heavy weight lifted on what I have to carry as a parent. This has eradicated the fear of wondering what [patient] may lose from one day to the next.” - Patient expert submission 2 (carer for a child with SMA)

[REDACTED]

13.5.14 Need for invasive or non-invasive ventilation

Inherently related to respiratory function, SMA can lead to a need for either invasive or non-invasive ventilation. For some people, ventilation may be permanent. However, there were some occasions where people talked about the need for ventilation, particularly from carers of children. One case study from a carer of a child, submitted as part of the appendix from the SMA UK/ MD UK/ Treat SMA joint organisation submission, noted that their child was intubated a month after being born and was offered OA despite managing only eight hours without Bilevel Positive Airway Pressure (BiPAP) per day. Patient expert submission 3 also noted that their child was dependent on a BiPAP ventilator during the night.

Receiving treatment was noted to either improve the amount of time or type of ventilation needed by people with SMA. One carer, quoted as part of the appendix from the SMA UK/ MD UK/ Treat SMA joint organisation submission, noted that while their child had previously been intubated every time they caught a common cold, receiving treatment meant that they could manage colds at home with the help of chest physiotherapy and BIPAP. An adult noted that their treatment had greatly reduced their reliance on ventilation, from permanent to only during the night.

“I was ventilated 24 hours a day just to stay alive I now only need my ventilator when I’m asleep and can mange all naps off it.” - Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with SMA

[REDACTED]

Despite the noted effect of treatment on the need for ventilation, the submissions also raised specific issues relating to the accessibility of treatments when a person with SMA is ventilated. A clinical expert submission noted that people who are long-term ventilated are currently ineligible via the MAA. They argued that this denies these people a meaningful quality of life, given that long-term ventilation does not necessarily mean they are not independent. This sentiment was echoed within a patient organisation submission. A carer, quoted in a patient organisation submission, summarised their experience of having to fight to have their child with Type 1 SMA given treatment due to being intubated.

“Being a young parent and having a recent diagnosis of SMA 1 is stressful enough on its own without having the fight we have to go through. Due to my little girl being intubated no treatment was available until we pushed and pushed and eventually got a trial for 3 months of risdiplam (which has worked wonders) now because my daughter is still intubated and the 3 months is nearly up we have to wait for it to go back to a panel meeting to see if treatment can carry on. It is so so disappointing as a parent to have to fight so much” - Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; carer for a child with SMA Type 1

13.5.15 Patient choice

The need for patient choice between different treatments links closely with the idea that the nature of SMA can vary between different types and SMN copy numbers, as described in ‘Spectrum of SMA’. The need for patient choice arose in the qualitative analysis for different reasons. A submission by a clinical expert noted that potential reasons for discontinuing or switching treatments include no perceived response to treatment and increased burden on both patients and families. The Association of British Neurologists noted that choice between nusinersen and risdiplam was essential because of side effects and the potential impact on fertility. The joint submission by SMA UK, MD UK and Treat SMA also noted that choice of treatments was important because different people will respond to treatment in different ways.

“It is important for the SMA community to have a choice of all available treatments on the NHS. There is not one treatment that is effective for all, both clinical and real world evidence has shown that there are non-responders to all of the treatment options, where one treatment is ineffective, another might get better outcomes. Choice and trial and error is currently the only way to optimise treatment outcomes for SMA.” - SMA UK/ MD UK/ Treat SMA joint organisation submission

In discussion with the EAG, representatives of patient organisations emphasised that “choice is key in the SMA community.” People with SMA and carers also expressed the need for patient choice when considering treatment options. They stated reasons for why people may choose different treatments, including echoing issues surrounding perceived lack of efficacy, the potential for adverse events, and being acknowledging individual lifestyles and preferences. Alongside this, patient experts consistently highlighted the need for treatment choices for people with SMA.

“Every patient should be given the right to receive treatment in a way that best suits their own personal circumstances and lifestyle choices.” - Patient expert submission 1 (adult with SMA)

“It is important that all three treatments are available. Firstly, so people have the right to choose their treatment. Secondly, to swap treatments if one no longer works, if there are any side

effects and if administering the drug is impossible via lumbar puncture. The right to choose is very important.” – Patient expert submission 2 (carer for a child with SMA)

“The perspective of the impact of treatment on daily life and quality of life is subjective and another reason for the importance of choice. Having three treatments available means that if a person does not get on with one or cannot have it there is the option of the other. For [patient] it will be vital that if his spinal curvature or any surgery prevents the use of nusinersen, he still has the option of risdiplam.” – Patient expert submission 3 (carer for a child with SMA)

13.5.16 Psychological impact

The physical symptoms of SMA and its impact on daily life were often cited as having a profound psychological impact on people with SMA, their families and carers. People noted that, although SMA is a physical condition, the impact on mental health and wellbeing could not be ignored. Stress and anxiety were often associated with having the condition.

[REDACTED]

Sometimes these feelings co-existed with feelings of anticipatory grief, fearing for what functions may be lost next. One adult described their fear of having a fall in a public space.

“That caused me quite a lot of stress and anxiety thinking, if I’m going to public places, what would I be able to do?” – Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with Type 3 SMA using nusinersen

[REDACTED]

The psychological impact on the family and carers of people with SMA was equally pronounced across submissions. A submission by patient organisations noted that, from a survey they conducted, 67% of carers reported feeling occasionally or frequently anxious, stressed or down because of their role. Carers for children with SMA expressed a range of emotions associated with the responsibility of looking after a child with the condition, including that the diagnosis is “devastating”, that they feel guilty that they are not doing enough to help their condition, and the immense stress of being a sole carer. Some carers turned to health services for support with their mental health, though there was some suggestion that this was not always available or offered.

“Living with a child with SMA is emotionally draining, I have recently contacted the doctor for counselling and treatment for stress and anxiety. It is a constant worry about the future and his independence.” – Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; carer for a child with Type 2 SMA (unknown treatment)

“We have not had any support for our mental health.” – Patient expert submission 3 (carer for child with SMA)

The wider family beyond those caring for people with SMA also described being affected psychologically and emotionally by having a family member with the condition. A submission from patient organisations noted that siblings reported feeling anxious and worried like the primary caregivers, but that they also feel that they receive far less attention from their parents as a result.

“I treat him like a normal brother. But it does make me sad that he cannot eat or walk and run. When he is poorly in hospital, I do feel very sad and worried, and I miss my mum a lot” - Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; 10-year-old sister of child with SMA.

Although treatments for SMA are not designed to improve mental wellbeing, the benefits it brings to physical health were described as having a subsequent positive impact on psychological health. Even if treatment is not designed to cure or improve SMA, the stability surrounding the physical symptoms of the condition it provided helps to alleviate anticipatory grief and provides positivity and hope for the future.

“In terms of the emotional/mental health aspect, the benefits are immeasurable. While I acknowledge the treatment is unlikely to provide me with significant improvements in my condition, the fact that I can now look forward to stability and maintaining my current levels of energy and strength has had unbelievable impact on my mental health.” – Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult (SMA type and treatment unknown)

These positive impacts on psychological wellbeing were also described by the families and carers of people with SMA.

“I do get time to socialize I am more mindful to enjoy myself because as the back of my mind I know my child is having treatment & it is a positive impact. I feel if [child] was not on any treatment, fear, anxiety would over take me and I wouldn't be able to enjoy to socialize as much.” – Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; carer of child with SMA

“If she was not on any treatments I would feel anxious and depressed - especially if I could see her declining. Her day to day care is something I don't choose to feel sad about - I remain positive and love watching her thrive. Her happiness and positive development through treatment has and IS helping me to be a strong, happy positive Mummy.” – Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; carer of child with SMA

[REDACTED]

13.5.17 Quality of life

Like independence, QoL is a theme that cross-cuts all aspects of the lives of people with SMA and those of their families and carers. For example, as stated within the submission by the

Association of British Neurologists, being able to maintain motor, bulbar and respiratory function all have a significant impact on QoL for people with SMA. However, a survey of both people with SMA and their carers conducted by SMA UK, MD UK and Treat SMA as part of their joint submission noted a range of potential reasons why someone's QoL may be impacted. The themes from their analysis of the free-text data differed between people with SMA and carers. From free-text submissions to their work, increased independence (including in work and their social lives) was the most frequently-cited way in which the QoL of people SMA was said to be impacted (N=23). By contrast, carers perceived that physical health may have had the greatest impact on the QoL of people with SMA (N=37).

There were also some specific examples of people with SMA and their carers talking about the impact of the condition on their QoL within the submissions.

[REDACTED]

As may be expected given the effects on outcomes such as motor, bulbar and respiratory function, people within the submissions highlighted beneficial impacts on their QoL from receiving treatment. The Association of British Neurologists and the submission to NICE from SMA Reach UK both stated that they expected the HRQoL of people with SMA treated with the technologies to increase in comparison to current care. The Association of British Neurologists also noted that, from real-world experience, the QoL of around 50% of patients was positively enhanced due to improvements in function and fatigue.

Individuals with SMA and their carers also noted the specific effects of nusinersen and risdiplam on their overall QoL. Sometimes this was linked to an improvement in physical function.

[REDACTED]

This was summarised in a quotation from an adult with Type 3 SMA.

“What that data collection fails to capture is the global impact of treatment on the patient. This is not just a ‘slicing up’ of motor functions, or distanced walked, or coins picked up. Rather it is something greater than the sum of its parts - a life lived better and longer, with less fear, less risk, less pain.” Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with Type 3 SMA being administered nusinersen

Representatives of PPI groups in their first discussion with the EAG noted that QoL was often improved in-between motor milestones, such as the ability to be able to use an electric wheelchair independently rather than be dependent on a carer. This was reflected in a submission from a clinical expert, who also highlighted that even if clinical scales did not detect any significant changes in function, patients often reported an enhanced ability to undertake activities of daily living, which in turn impacts QoL. Professionals speaking with the EAG also noted that, although there are more recent initiatives to collect data on outcomes that may impact QoL, this may not be reflected in current data.

13.5.18 Spectrum of SMA

The qualitative data highlighted a strong emphasis by patient and professional groups on the heterogeneity across the spectrum of SMA. Some submissions emphasised the differences in trajectory of the condition, even between individuals who have been diagnosed with the same SMA type and have the exact SMN2 copy numbers. This was summarised in discussions between representatives of patient groups and the EAG.

“The spectrums are so big now. So even with a type 1, a, a type 1 to a type 1 is very, very different. At type 2 to a type 2 is very, very different. So where [patient] is talking about some of the, you know, aspirations and hospital visits, etc. My kids who have type 2 have a very, very, very, very different type of experience and have none of that. So I think it just needs to be wind into that narrative that the spectrum is massive.” - Patient group representative in discussion with the EAG

It was also noted by representatives of patient organisations that treatments do not impact individuals with SMA in the same way, and that there was not “one drug fits all SMA.” It was also noted by a joint submission to NICE that the effectiveness of treatment may differ between individuals with similar clinical features, underscoring the importance of ensuring that clinicians and patients have access to both treatment options.

“The data collected as well as experience supporting people through patient organisations, shows that the treatments do not impact individuals living with SMA in the same way. Two individuals with the same SMN2 copy numbers and presenting similarly clinically will not necessarily have the same treatment outcomes. For a minority of individuals, 2 in our data sample, treatment is not effective, or side effects decrease quality of life.” - SMA UK/ MD UK/ Treat SMA joint organisation submission

There was also concern that the diversity of the patient cohort meant that the assessments used to measure function, particularly motor function, were not sensitive enough. The submission by the Association of British Neurologists noted that there was no “single fit-all outcome measure to apply across the disease spectrum to define a clinically significant response to treatment.” The challenge of defining a clinically significant result for such a diverse cohort of patients was raised by the Adult SMA Reach submission, who noted that benefit from treatment can be variable as a result.

“The benefit is variable and outcome measures used in the MAAs may not capture all and consideration should be given to the challenges of the vast disease spectrum.” – Adult SMA Reach submission

13.5.19 Stamina and fatigue

The importance of the impact of SMA on stamina and fatigue to individuals is reflected in the regularity with which it is discussed for both adults and children. Patient experiences related to fatigue and stamina were varied, with some patients reporting its impact on activities of daily living such as ability to communicate and being able to talk more frequently without running out of breath when on treatment and being able to maintain employment and education.

“I was really tired every day, I found it really difficult to get out of bed, I didn’t really know what my fatigue level would be from day to day, what I wanted to do or what I could do. That provided a lot of uncertainty for me.” - Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with Type 3 SMA being treated with nusinersen.

“I had little energy, little strength, I was struggling to drive my wheelchair and got extremely tired and suffered from extreme fatigue even just working for short periods.” - Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with an unknown SMA type being treated with risdiplam.

As well as the direct impact of SMA on patients’ energy levels, the condition was also reported to affect the energy and stamina of the carers who support their loved ones. Many carers reported feeling overwhelmingly tired and emotionally drained due to the constant demands of ensuring the needs of the person they are caring for are fully met, as well as the broader impact in terms of strained relationships with other family members, such as their partners or other children.

“Tiredness is overwhelming and leaves you feeling it is too much effort to do anything else but care for your loved one.” – Quotation from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; carer for a child with SMA.

“Exhausting always being the sole carer to someone” - Quotation from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; carer for a child with SMA

The submission by the Association of British Neurologists indicated that one of the primary aims of treatment with both risdiplam and nusinersen and a clinically relevant treatment response is to improve levels of fatigue, subsequently improving quality of life. The Association of British Neurologists also confirmed a general positive experience in adults, with approximately 50% of patients experiencing improvement in function and fatigue. This reported improvement was further reflected in the qualitative data, with many adults receiving both nusinersen and risdiplam mentioning increases in energy and a drop in fatigue,

[REDACTED]



Throughout the various evidence used for the qualitative data analysis, including patient submissions, professional submissions and PPI group transcripts, stamina and fatigue were frequently referred to as a clinically relevant and highly meaningful outcome measure for adults and children across all types of SMA. Representatives of patient organisations told the EAG that stamina and fatigue were important outcomes to measure. In discussion with the EAG, professionals noted that there is ongoing work within the community to attempt to capture data on stamina and fatigue. This includes the EK-2, while the SMA EFFORT scale to capture perceived fatigue was also mentioned. In addition, a clinical expert emphasised in discussion with the EAG the importance of differentiating between perceived fatigue and performance fatigue.

Despite this, it was also said to the EAG that data surrounding stamina and fatigue were often not captured and that there are gaps in the evidence surrounding these outcomes. The submission by SMA Reach UK also noted that although fatigue was an important outcome, this is not captured within trials.

13.6 Key/summary effectiveness results

The evidence for the effectiveness of both nusinersen and risdiplam was found to be uncertain and at moderate risk of bias, mostly due to the small proportion of randomised controlled trials and other controlled designs. It should also be noted that little or no evidence was found concerning type 0 or type 4 SMA. However, with these caveats the EAG concludes the following.

The evidence suggested that nusinersen improved or maintained motor function on average across SMA types for up to five years. Some studies reported differences in effectiveness

between population subgroups in relation to age and SMA type. Favourable results were also reported in relation to mortality, with higher survival rates amongst nusinersen-treated patients overall, especially for type 1 where children would usually survive no more than a few months without treatment. Stability or maintenance in respiratory function was generally suggested. Mixed results were reported regarding the effects on bulbar function and quality of life of carers and SMA patients. The long-term safety profile of nusinersen was found to be favourable, across a large number of real-world studies. Most adverse events were attributed to the injection or the disease, rather than the drug itself.

For risdiplam, patients continued to improve or maintain their motor function in all measures for all SMA types included. There was mixed evidence for the effects of risdiplam on bulbar function and ventilation. Evidence suggested maintenance or small increases or decreases in respiratory function, although the evidence was sparse. Due to the lack of controlled studies, the evidence on mortality was limited by the inability to compare longevity between people who were and were not treated with risdiplam. Adverse effects were generally not serious.

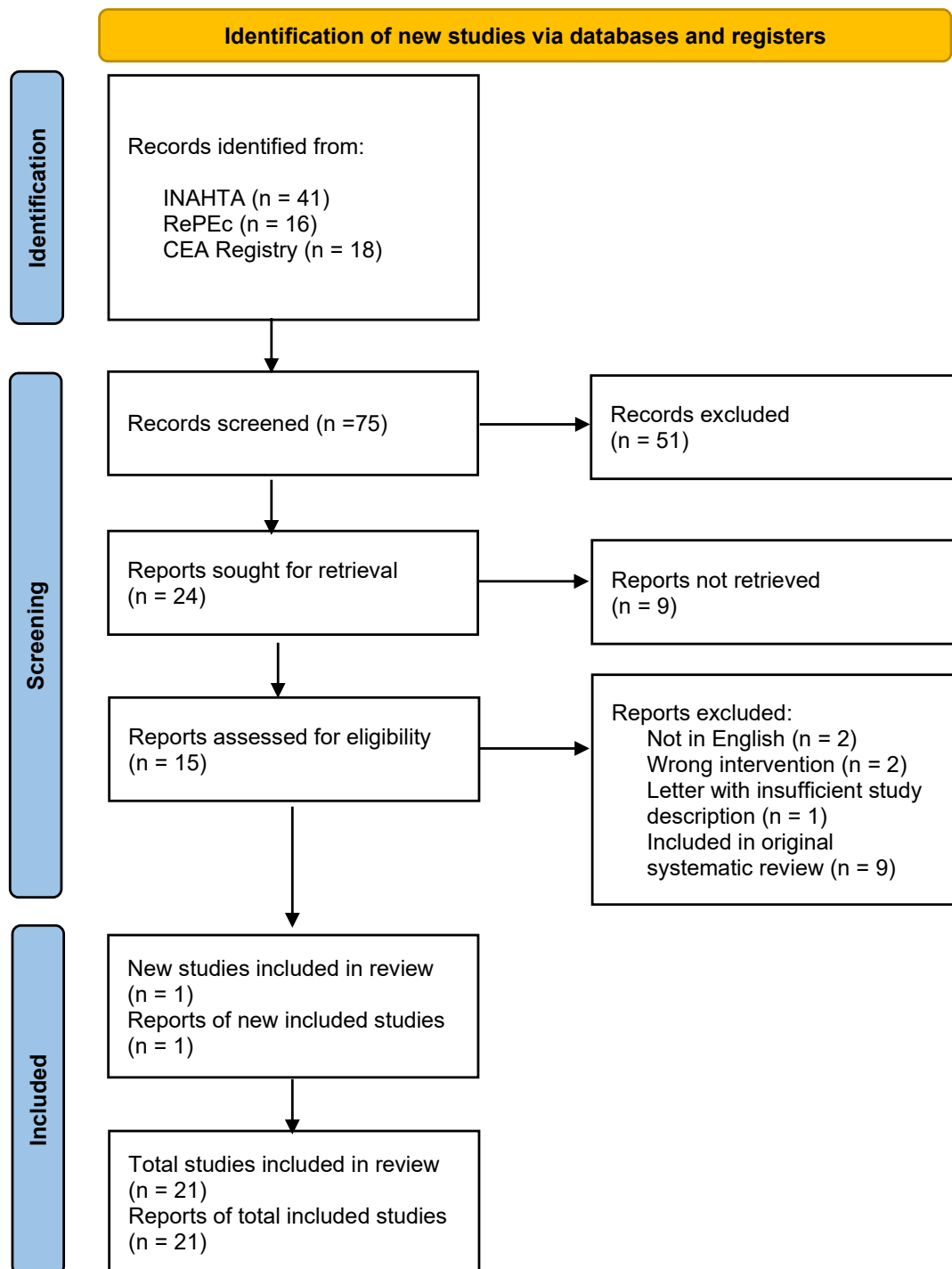
From the limited evidence available, nusinersen and risdiplam appeared to have comparable efficacy, although study limitations (e.g. baseline imbalances in prognostic factors) undermine the comparability of the data.

The MAA data showed a similar picture, suggesting that treatment with both nusinersen and risdiplam lead to maintenance or improvement for motor outcomes, across all SMA types assessed. From the paediatric registry, nusinersen had longer follow-up data available than risdiplam for motor outcomes (~4+ years vs ~1.5+ years, respectively). While the adult registry for risdiplam extended to ~4 years, the patient numbers were smaller at this point than those in the nusinersen MAA. This is to be expected given that nusinersen was available earlier. Data for patient-reported outcome measures was lacking for both treatments and suggested some varying results. However, maintenance or improvement was reported for some scales for both nusinersen and risdiplam. Similarly, for both treatments separately, data surrounding QoL were also lacking but did suggest some improvement. Importantly, mortality rates in the MAA were generally low for both treatments and deaths that did occur appeared to be unrelated to the treatments.

14 EAG cost-effectiveness SLR: results

In the previous systematic review, 920 records were identified through database searches, while none were identified through other sources. After deduplication, 694 records were screened at title and abstract stage, out of which 71 records were assessed for eligibility at full text. In total, 20 records were considered relevant and included in the previous systematic review.

In this review update, 75 additional records were retrieved from databases searches for relevant economic evidence post-January 2025 to present. No duplicates were identified. At the title and abstract screening stage, 24 records were included as potentially relevant. At full text screening, one record was identified as new relevant evidence, while the remaining 23 records were excluded. The flow of records is depicted in Figure 33, with reasons for exclusion at full text.

Figure 33: PRISMA diagram for updated economic SLR**14.1 Characteristics of included studies**

A summary of the characteristics of included studies in the previous SLR and in this update are provided in Appendix (see Appendix 7, Section 19.7).

In the original SLR, 20 economic analyses were included. This focused on patients with presymptomatic SMA, types 1, type 2 and type 3 SMA. There were no evaluations focusing on patients with type 0 or type 4 SMA. Across the included analyses, study populations and

subgroups were defined by the type of SMA, number of SMN2 gene copies, age of diagnosis or disease onset, duration of disease and treatment received.

In this review update, the one study included was a cost utility analysis by Khuntha et al. 2025²⁴² which focused on symptomatic SMA patients in Thailand. Patients were categorised into two groups: 1) SMA type 1 age onset at 3 months, and 2) SMA type 2 age onset at 12 months, and SMA type 3 age onset at 18 months, based on disease severity and treatment indications.

14.2 Intervention(s), comparator(s), outcome(s), study perspective, location and setting

In the initial SLR, the studies included reported costs for the following treatment comparisons:

- **OA versus BSC:** Ellis et al. 2019,²⁴³ CADTH-OA, 2021,²⁴⁴ Broekhoff et al. 2021,²⁴⁵ Connock et al. 2020,²⁴⁶ Dean et al. 2021,²⁴⁷ Meijer et al. 2023,²⁴⁸ Wang et al. 2022.²⁴⁹
- **Nusinersen versus BSC:** NICE-TA588,² Ellis et al. 2019,²⁴³ CADTH-OA, 2021,²⁴⁵ Broekhoff et al. 2021,²⁴⁵ Connock et al. 2020,²⁴⁶ Wand et al. 2022,²⁴⁹ Zuluaga-Sanchez et al. 2019,²⁵⁰ Thokala et al. 2020,²⁵¹ NCPE-2017,²⁵² CADTH-Nusinersen, 2019,²⁵³ SMC-Nusinersen, 2018.²⁵⁴
- **Risdiplam versus BSC:** NICE-TA755,³ CADTH-risdiplam, 2021.²⁵⁵
- **OA versus nusinersen:** NICE-OA HST 51,²⁵⁶ Broekhoff et al. 2021²⁴⁵, SMC-OA, 2021,²⁵⁷ Connock et al., 2020,²⁴⁶ Dean et al. 2021,²⁴⁷ Malone et al. 2019,²⁵⁸ Wang et al. 2022.²⁴⁹
- **Risdiplam versus nusinersen:** CADTH-risdiplam, 2021,²⁵⁵ SMC-risdiplam, 2022.²⁵⁹

Across the included studies, the focus was on the health benefits in terms of LYGs and QALY gains. The study locations were located globally, including in the USA, UK, Australia and Canada, and all the studies were from high-income countries. Apart from SMC-risdiplam, 2022²⁵⁹, all other studies adopted the viewpoint of the health system, societal perspective or both.

While all studies included in the previous SLR were all undertaken in high-income countries, Khuntha et al. 2025²⁴² included in this SLR update, evaluated the cost-utility of OA and risdiplam compared with SoC for SMA in Thailand (a middle-income country), thus providing some context for Southeast Asian and middle-income countries. Lifetime costs and outcomes expressed as QALYs gained were presented from both the provider and societal perspectives, which incorporated direct medical and non-medical care costs, as well as indirect costs incurred by caregivers.

14.3 Model structure and health states

All 20 studies included in the original SLR presented Markov models to simulate patient treatment outcomes for SMA and analyse the cost-effectiveness of the treatments for SMA. Half of the included studies included a single Markov model for the cost-effectiveness analysis,^{244-249,251,256-258} while separate Markov models for assessing type 1 and type 2/3 SMA were used in seven included studies.^{2,3,250,252,254,255,259} Furthermore, separate Markov models were also used in the NICE HST 24 surrounding treatment with OA¹⁶ for modelling short- and long-term analyses, based on available trial data and the extrapolation of data respectively. In ICER 2019,²⁴³ three separate Markov models were employed for patients with presymptomatic, type 1, type 2/3 SMA, while CADTH Nusinersen-2019²⁵³ included three

distinct models to evaluate the cost effectiveness of treatments for type 1, type 2, and type 3 SMA.

In most of the studies included in the original SLR, the health states were defined by functional milestones (e.g. sitting, standing, walking, and ventilation support) which are indicators of functional abilities, disease progression and severity in SMA patients. Death was included as an absorbing state in all these models.

Comparable to the economic evaluations in the original SLR, in the new included report, Khuntha et al. 2025²⁴² constructed a Markov model to simulate the progression of SMA based on level of motor functioning, as measured by the CHOP INTEND. The model comprised the following five health states: a broad range of normal development; walking with support or equivalent; sitting; not sitting but living ventilation-free; and permanent assisted ventilation. These could all lead to the absorbing death state. To be consistent with the nature of the disease, patients entering the model could start at any health state except death. The models described the direction of health state transitions, which depended upon the treatment received.

14.4 Time horizon, cycle length and discount rate

The economic analyses conducted in the initial SLR considered life-long time horizons ranging from 60 years^{2,244} to 100 years.^{16,256} These studies attempted to capture the long-term effects of interventions in SMA patients in terms of the costs incurred and the benefits acquired through treatments. Meanwhile, some economic evaluations covered shorter-term time horizons like 36 months²⁴⁸ or 25 years.²⁵³ These variations in time horizon indicated the different approaches adopted by decision modellers to assess the cost effectiveness of SMA treatments.

Most of the included studies clearly stated that the costs incurred, and the benefits acquired over time were discounted with the annual discount rate varying between studies between 1.5% and 5%.^{244,249} Therefore, some of the difference in costs and benefits between studies was a result of the choice of discount rate used.

The cycle length of the economic analyses in the included studies also varied, reflecting the dynamic nature of SMA disease progression and treatment outcomes. This largely depended upon the type of SMA, treatment intervention and specific trial endpoints (if trial data were considered). These were shown to vary from one month to specific time-periods to assess the treatment effect, which coincided with trial endpoints, with some modelled for up to a year. This further complicates comparisons between the results of different studies.

In the one study identified in the SLR update by Khuntha et al. 2025²⁴² the economic model generated included a lifetime horizon to capture the long-term benefits of the treatments. Additionally, as recommended by Thai HTA guidelines, a 3% annual discount rate for both costs and outcomes was applied. A six-month cycle length was also assumed based on the natural history of the disease and as defined by the CHOP INTEND.

14.5 Health state utility values

The health state utility values (HSUVs) used in the economic analyses in the original SLR were informed by various sources, such as literature reviews, expert opinions and clinical data from trials and registries. The values were assigned specifically based on the health states and the definition of these health states, which introduced some variability because of the difference in sources of evidence used to inform these health states. Additionally, some

studies favoured expert opinions while others relied more on the use of published literature or clinical data. Hence, there were differences in approach between studies as to the type of empirical evidence reinforcing the health state utilities of patients with SMA. Across the studies, the obtained values were regularly mapped to the EQ-5D, which demonstrates a standardised approach in the evaluation of health benefits of SMA treatments, making it easier to make comparisons between the utilities used across these studies.

Among the studies from the previous SLR, 5 studies included carer disutilities. But there were considerable differences in terms of the methods and data sources used to obtain the caregiver specific utilities, to incorporating caregiver utilities into the SMA models. NICE TA588 and TA755 considered the quality of life of caregivers by applying a utility decrement relative to the general population by comparing the utility estimates against a population score.^{2,3} Meanwhile, CADTH-Nusinersen did not include caregiver utilities in its submission.²⁵³ SMC-Risdiplam, 2022 sourced the burden on caregivers from published literature and relevant NICE submissions.²⁵⁹ NICE HST24 used extensive expert opinion analyses and clinical trial data to source the carer utilities in SMA models.¹⁶ NICE HST15 explored the caregiver burden and its effect on their quality of life by modelling a scenario analysis.²⁵⁶ The methods adopted in these studies gives an insight into the relevance of clinical data, how comprehensive these are in capturing the quality of life of caregivers with respect to the changes in patient health states, and the importance of eliciting expert opinions to substantiate caregiver utility estimates. The inferences drawn from these studies can help researchers make informed decisions about assumptions around the factors and considerations that can potentially influence the treatment outcomes in SMA patients.

The cost utility analysis identified in this SLR update utilised the EQ-5D-Y-3L questionnaire, translated into Thai, to interview patients and caregivers.²⁶⁰ In the absence of an EQ-5D-Y valuation study for Thailand, the authors calculated utility values using a Japanese value set. However, due to a limited number of patients for two health states, utility estimates from a Chinese study, which used EQ-5D-3L for patients with SMA types 1-3, was used as proxy.

14.6 Health state resource use and costs, currency and conversion

In the original SLR, the data sources used in the included studies to obtain the resource use and costs were real-world evidence (e.g. national health services), clinical trials, and studies that evaluated healthcare resource utilisation in patients with SMA. The external validity of these figures for resource use and costs were then ensured through literature reviews and experts' opinions in majority of these studies.

NICE TA588 used Hospital Episode Statistics (HES) in the UK and SMA linked direct expenses in the UK healthcare system to estimate resource use and cost.² TA755 adopted the resource uses associated with the health states from NICE TA588,² as well as unit costs from the NHS. SMC-OA 2021 obtained costs from the Scottish Health Services Cost,²⁵⁷ while Wang et al., 2022 used cost estimates from Australian national health services data in cost-effectiveness analysis.²⁴⁹ As such, these studies undertook an approach where region specific data on cost from the national health services were deemed appropriate. CADTH-Nusinersen, 2019 derived costs from Klug et al,²⁶¹ a study of the economic burden of SMA in Germany,²⁵³ while SMC-risdiplam 2022 used data from real-world evidence studies by the respective companies.²⁵⁹

The sources of data used for estimating costs in these studies varied based upon the setting of the study, availability of data and study perspective. In the majority of the studies, there has

been a conscientious effort to adapt the national health services or local health services data for estimating cost. Where there was a lack of sufficient evidence, the studies relied on published literature, studies from pharmaceutical companies, or expert opinion.

The analysis of cost in the included studies showed variation in terms of the granularity of how costs were broken down. Some studies used detailed cost breakdowns with respect to different components and items, while others reported more aggregated cost estimate. In studies like NICE TA755,³ costs were applied universally in the BSC arm and a part of the intervention arms, wherever applicable. Across the studies, researchers can understand the existing methodologies and criteria on estimating cost of SMA treatments, through the differences in sources informing the costs, methods of cost estimation in model and cost conversion practices in countries like UK, Australia and Canada.

Similar to studies included in the original SLR, the new study, Khuntha et al. 2025²⁴² obtained resource use and costs primarily from real-world evidence. Interviews with Thai patients provided information on resource use and costs incurred by patients and carers, while direct medical costs were retrieved from hospital databases and pharmaceutical companies. The lower price of OA used in this study was reported to be like that of a similar study in Brazil, and thus was thought to be a reference price for middle-income country settings. Costs input into the model were reported transparently, broken down by parameter and calculated for each health state in each SMA subtype. The consumer price index was used to adjust all costs to 2023 values and the recommended WTP threshold of 4444 USD per QALY gained was applied, which equated to 160,000 Thai baht per QALY gained using an exchange rate of 1 USD ≈ 36 Thai baht.

14.7 Results of engaging patients and stakeholders

In the original SLR, it was noted that across included studies the methods and extent to which engagement with patients and stakeholders occurred, varied between different locations and the established review systems. The incorporation of patient and stakeholder perspectives highlighted the commitment to include those impacted by SMA in the assessment and reporting process.

While not stated to be involved in the utility value estimations, patient and carer groups were reported to participate and provide their insights during the assessment processes for TA588,² TA755,³ HST15,⁴¹ and HST24.¹⁶ Additionally, in ICER-2019,²⁴³ patients were directly involved in the discussion at early stages of the study. In some evaluations, for example SMC-risdiplam-2022,²⁵⁹ patient groups and clinicians contributed to assessing the value of risdiplam, while in others like SMC-nusinersen-2018²⁵⁴ and SMC-OA-2021,^{254,257} patient group representatives were engaged in the evaluation of the additional benefits of SMA treatment. Inputs from patients were directly obtained in the CADTH-risdiplam-2021²⁵⁵ through the standardised CADTH review process,²⁵⁵ while in CADTH-OA-2021 surveys and semi-structured interviews were employed.²⁴⁴

In the cost utility analyses by Khuntha et al. 2025²⁴² newly identified in this SLR update, the authors conducted interviews with Thai patients and caregivers to collect data on transitional probabilities, non-medical costs and utilities. Additionally, as a form of face validity testing, consultation meetings with stakeholders took place to consider the proposal, model, conceptualisation, input parameters and preliminary results of the study. Although some outcomes from the meetings were described, a complete account of the meetings, including all attendees, was not provided.

14.8 Results of resource use and costs

In the original SLR, the included studies indicated a range of approaches used for resource use and costs in modelling of the economic burden of SMA, which reflected the study contexts and highlighted the complexities and nuances in treating patients with SMA.

TA588 included the itemisation of cost based on categories such as drugs, medical tests, hospitalisations and social services.² The cost analysis in TA755 was adapted from the TA588 real-world evidence study, which provided cost data based up expert opinion of clinicians.^{2,3} Both Zuluaga-Sanchez et al. and NCPE-2017 undertook a similar approach by focusing on health-state costs, drug-acquisition and related costs.^{250,252} However, some studies like SMC-Risdiplam-2022 and Malone et al. 2019 had their own unique perspective on resource use and subsequent estimation of cost.^{258,259} Wang et al. focused on drug-acquisition and monitoring among health states,²⁴⁹ while Thokala et al. leaned towards resource allocation and treatment costs.²⁵¹

In the review update, Khuntha et al. 2025 calculated lifetime costs for each SMA subgroup (type 1 and types 2/3) from the provider perspective, which included only direct medical costs in current practice such as disease diagnosis, assistive equipment and medication costs during ambulatory care and hospitalisation.²⁴² Moreover, lifetime costs from the societal perspective were estimated, which in addition to direct medical costs included direct non-medical costs incurred by patients and caregivers, as well as indirect costs including other out-of-pocket charges for informal care and productivity costs from caregivers.

14.9 Results of survival modelling

In the previous SLR, it was noted that the methods used in the included studies for estimating the survival in patients with SMA varied based on the type of SMA and data availability. Furthermore, the range of unique and complex strategies adopted in the survival analysis of patients, reflected the complexity of treatment and dynamic nature of the patient disease conditions that were considered in modelling survival outcomes for patients with SMA.

For example, TA588 adopted different approaches for type 1 SMA and type 2/3 SMA.² In type 1 SMA, flexible spline Weibull models were used for extrapolating the overall survival while in type 2/3 SMA, 2 knot spline flexible models were used. This was based on the best fit on the trial data. The end-of-life criteria were applied with an adjustment factor of 0.75. NICE TA755 adopted a similar approach to modelling survival estimates in SMA patients.³ The latter used two different approaches to model survival of patients with type 1 and type 2/3 SMA. Based on trial data, different models were used on data from the two trial arms (risdiplam and BSC) in type 1 SMA, an exponential model was applied to the risdiplam group and an indirect hazard ratio (HR) comparison for various health conditions was used for the BSC group. For type 2 SMA, parametric models were fitted to pseudo-IPD data, while in type 3 SMA, the mortality rate was considered similar to that of the general population. Furthermore, a HR of 0.75 was applied to the intervention arm of type 2 patients to reflect the likelihood reduction of mortality associated with treatment, which was also adopted in TA588.²

The long-term survival estimates for patients with SMA in HST24 involved using the standard methods of fitting parametric models to data from natural history studies and UK National life table data.¹⁶ Additional assumptions from HST15 and clinical expert opinion were also adopted to prevent having clinically implausible survival estimates.²⁵⁶

In the cost utility analyses by Khuntha et al. 2025²⁴² identified in the SLR update, parametric survival curves were modelled to extrapolate lifetime transition probabilities for each health

state transitions under SOC based on medical records from one of the largest Faculties of Medicine in Bangkok, Thailand (n=114 patients with SMA from the first diagnosis in 1999 to the current diagnosis in 2021). The Akaike information criterion, the Bayesian information criterion, and a visual inspection of fit were the methods used to select the appropriate distribution. The Weibull and Gompertz distributions for SMA type 1 and types 2–3, respectively, were deemed the most appropriate fits. Calculation of health state transitions and mortality with OA and risdiplam treatment used unpublished and published clinical trial data.

14.10 Assumptions used in studies and reports

In the previous SLR, a range of assumptions based on common themes were identified in the included studies and were centred on the survival of patients, mortality risk, motor milestones and its sustainability, disease progression, treatment effects and discontinuation, patient/caregiver utilities and treatment/monitoring cost. The implementation of these assumptions varied among the SMA models and was based on the study perspective and availability of real-world data. The individual patient-level data on various aspects of SMA treatments are scarce because of the nature of the disease and characteristics of the patient population and, this was a limitation that was observed across the included studies.

In TA588,² several assumptions around patients' mortality, trial duration, treatment response, utility estimates, scoliosis surgery and data sources were made. TA755 established assumptions about utility values, carer disutilities, complications and treatment costs.² The assumptions made in HST15 were around carer disutilities, milestones and transition of patients among health states;²⁵⁶ HST24 maintained these assumptions in its cost-effectiveness analysis.¹⁶

CADTH-Nusinersen, 2019 implemented modelling assumptions regarding the disease progression, treatment discontinuation and the mortality in patients with SMA.²⁵³ The CADTH-Risdiplam, 2021 evaluation made several assumptions regarding the motor milestones in patients, treatment discontinuation, treatment outcomes and mortality risk in patients with SMA, based on the inputs from clinicians and patients.²⁵⁵ In the evaluation CADTH-OA-2021,²⁴⁴ assumptions adopted included those regarding motor milestones, risk of mortality, health states associated patient transitions, permanent ventilation as a health state and monitoring costs. In SMC-Nusinersen-2018,²⁵⁴ treatment discontinuation, treatment effects post discontinuation and mortality were the areas of focus for making assumptions. SMC-OA-2021 incorporated scenarios about age-appropriated motor milestones in presymptomatic and symptomatic SMA patients, treatment efficacy and discontinuation assumptions.²⁵⁷

Wang et al. made assumptions about patient transitions among the health states, survival of patients, sustainability of motor milestones, patient utilities and treatment administration duration in SMA.²⁴⁹ Zuluaga Sanchez et al. 2019²⁵⁰ integrated assumptions regarding, cost, health state utilities, continuation of treatment effects during follow-ups, mortality rates, caregivers, health-state costs, motor milestones and its impacts. Thokala et al. 2020 made assumptions about survival, costs, utilities, and whether the motor function milestones were sustained over lifetime, ventilations, patient transitions and disease progressions.²⁵¹ In Broekhoff et al 2021,²⁴⁵ key assumptions were made for health state maintenance and transitions, effect of motor milestones on survival, health-related quality of life and reversibility of health conditions. Malone et al. 2019 made assumptions with respect to the disease progression, milestone, lifelong treatment effects and treatment continuity.²⁵⁸

The one study added in the review update, Khuntha et al. 2025²⁴² used several assumptions around model structure in the cost-effectiveness analysis. For instance, the patients in the SoC arm would either be stable or experience deterioration in their health states. Other assumptions surrounded health state occupancy and transition of patients, mortality rates and that all patients who enter the model have their disease confirmed through genetic testing for SMA.

14.11 Model inputs used across studies

Across the studies included in the previous SLR, it could be inferred that the economic analyses collectively addressed variables and parameters, which are common factors associated with SMA and treatment pathways, across locations and local healthcare systems. The elements driving the model and explored in the cost-effectiveness analysis of SMA treatments included utility values, health state costs and risk of mortality.

For example, in terms of the UK perspective, TA588 and TA755 considered parameters such as health state occupancy and transitions, surgery and age at which surgery occurred, overall survival, utilities of patients and caregivers, cost associated with health states.² Malone et al. 2019 used similar model inputs for the cost-utility analysis, except that Malone et al. 2019 was from a US perspective.²⁵⁸ HST24 undertook a similar approach by modelling parameters like time horizon, health state utilities and costs, mortality risk and mean age of patients.¹⁶ The study by Zuluaga-Sanchez et al. 2019 followed a comparable approach as well, with emphasis on resource use and cost.²⁵⁰ Thokala et al. 2020 and Meijer et al. 2023 explored health state specific utility values, administration and monthly costs for SMA treatments.^{248,251}

Different model inputs included in Khuntha et al. 2025²⁴² were survival estimates of SMA patients, transition probabilities in the model, treatment effects, mortality risks, utility estimates and resource use and cost estimates (for middle-income countries). The healthcare costs included both direct and indirect medical costs, drug costs and cost of hospitalisation.

14.12 Characterising uncertainty in different studies

In the included studies identified in the original SLR, it was reported that uncertainties were addressed through a range of methods to quantify the effects of various parameters on the cost-effectiveness result. TA588² and Zuluaga Sanchez et al.²⁵⁰ employed probabilistic sensitivity analysis (PSA) and different scenario analyses to characterise the uncertainties in their respective studies. Similarly, HST15,⁴¹ and HST24,¹⁶ CADTH-Nusinersen-2019,²⁵³ as well as CADTH-Risdiplam, 2021,²⁵⁵ undertook both sensitivity and scenario analyses to address the uncertainty around the results. TA755 and Wang et al. 2022 used both probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis (DSA) for analysing the uncertainties introduced by the parameters and variable.^{3,249} CADTH-OA-2021²⁴⁴ and SMC-OA-2021²⁵⁷ utilised numerous scenario analyses while, Thokala et al.²⁵¹ and Dean et al.²⁴⁷ used one-way sensitivity analysis (OWSA) and scenario analysis to study the variability in clinical benefits of treatment. SMC-Risdiplam-2022²⁵⁹ focused on different scenario analyses to demonstrate the intervention benefit over other treatments. Broekhoff et al. 2021²⁴⁵ and Malone et al. 2019²⁵⁸ used sensitivity and scenario analyses to investigate the impact of parameters in the model outcomes. In conclusion, the studies utilised various sensitivity analyses and multiple scenario analyses to characterise the uncertainties in the cost-effectiveness estimates.

Furthermore in the economic evaluation by Khuntha et al. 2025²⁴² identified in the SLR update, uncertainty was characterised using multiple sensitivity and scenario analyses. OWSA was

used to study the impact of variability of parameters on the ICER while PSA was utilised for assessing the uncertainties of all parameters. The effect of variation in treatment cost on ICER was observed by employing various scenario analysis.

14.13 Limitations identified across studies

Across the economic evaluations of SMA therapies conducted in the studies included the original SLR, several limitations and trends were identified, such as uncertainty in the clinical data available. In TA588² and TA755,³ there was uncertainty around clinical effectiveness of the treatments and evaluation of utility estimates. Similarly, NICE HST-15²⁵⁶ had limitations around the cost-effectiveness results due to uncertainty in the clinical data. NICE HST-24¹⁶ also presented uncertainties around clinical effectiveness due to a narrow range in age of participants in the clinical trial. SMC-Nusinersen, 2018²⁵⁴ had no long-term survival data from the trial which created uncertainties in the cost-effectiveness by overestimating the benefits. Thokala et al. 2020²⁵¹ had similar limitations due to lack of longer term follow-up data. The previous SLR also noted that bias due to the incomplete follow-up in survival data, presented uncertainty in the cost effectiveness estimates in SMC-Risdiplam, 2022.²⁵⁹

Zuluaga Sanchez et al. 2019²⁵⁰ was limited by a small sample size in the trial impacting the clinical outcome of the treatments, resources and cost data that impacts the cost estimation of SMA therapy. In Wang et al. 2022,²⁴⁹ there was a similar type of limitation arising due to lack of long-term data, while Dean et al. 2021²⁴⁷ had incomplete follow-up data resulting in uncertain cost-effectiveness estimates.

CADTH-Nusinersen-2019²⁵³ faced challenges around the uncertainty in utility estimates. Similarly, CADTH-OA-2021²⁴⁴ had problems with utility values and limited clinical data. For CADTH-Risdiplam-2021,²⁵⁵ comparative treatment benefits and modelling assumptions were sources of uncertainty. ICER 2019²⁴³ grappled with a lack of robust data which introduced structural uncertainty in the SMA models.

Meijer et al. 2023²⁴⁸ presented uncertainty in the model generated due to variability in patient characteristics. Moreover, Connock et al. 2020²⁴⁶ and Malone et al. 2019²⁵⁸ struggled with limitations in data availability. All the limitations discussed here were stated to reflect the lack of clinical data which underpins the complex methodologies and challenges faced when conducting economic evaluation for SMA treatments.

The major limitation of the Khuntha et al. 2025²⁴² identified in the SLR update was the small sample size of the study informing real-world clinical data. But this was understandable given the rarity of the disease. The clinical trial included one site, representing 50% of SMA patients in the country, and the results from this study were used to inform national policy on SMA therapy. Hence, there were concerns about the generalisability of the clinical effectiveness data of SMA treatments. Additionally, the study did not include the various adverse events from treatment, but it was assumed that its effect were captured in the medication costs and health state utility estimates of patients.

14.14 Reporting and methodological quality assessment

14.14.1 Reporting quality assessment

The quality assessment of reporting in the 20 studies in the previous SLR and in this SLR update were conducted using the CHEERS 2022 Checklist⁹⁵ and the results are provided in Appendix 8 (Section 19.8).

Most of the studies included in the original SLR were noted to have a clear structure in reporting with title, introduction, methods, results and discussion. Thus, the reporting quality of the studies were considered satisfactory. Many published studies had an abstract which included a summary with excerpts from all the different sections included in the content. While the included reports, most likely as it was not a prerequisite during their preparation, did not include an abstract.^{254,257,259} Although, these reports were noted to provide detailed descriptions about the economic analysis conducted, when compared to other published studies. Almost all the studies reported methods used in the economic analysis such as patient characteristics, location and settings, study perspective, comparators, choice of time horizon, measurement and valuation of outcomes.

Some studies did not score particularly well against the CHEERS 2022 checklist,⁹⁵ despite having detailed reporting on their methods and results, and was concluded to be because the studies lacked a health economics plan (HEAP), consideration of distributional effects or engagement with a patient population. These items were added as an update in CHEERS 2022⁹⁵ appraisal tool from its previous version.

It was also noted that the SMC reports did not provide adequate information on the description and justification for selecting the model, methods of analysis, as well as the statistical methods used for evidence synthesis and for characterising heterogeneity. While other studies did not have clear explanation about parametrisation and accounting for uncertainty introduced in the model.^{254,257} Overall, it was therefore reported that the included studies adhered to the CHEERS 2022 criteria⁹⁵ to varying degrees with some studies lacking in reporting of items recommended when preparing health economic evaluations.

Khuntha et al. 2025²⁴² had a clear structure in reporting with title, introduction, methods, results and discussion like the articles in the original SLR. When assessing specific sections, the article did not note that a health economics assessment plan (HEAP) was developed prior to conducting the analysis. It did not provide information about characterisation of distributional effects of individuals on impacts and lacked description about methods used to assess uncertainty introduced by heterogeneity.

14.14.2 Methodological quality assessment

The Philips Checklist⁹⁶ was used to assess the methodological quality of the 20 studies included in the original SLR and in the SLR update. The results are reported in Appendix 9 (Section 19.9). The articles, reports and supplementary papers or evidence that are publicly available as electronic evidence were used to apply the qualitative methods of assessment in the Philips Checklist.

From the included studies, those that performed best overall in the assessment were TA588,² HST24,²⁰⁴ and ICER Spinraza and Zolgensma 2019,²⁴⁷ in terms of quality of methodology and low risk of bias. While SMC Onasemnogene -2021²⁵⁷ and NCPE-2017²⁵² performed less well in quality assessment with respect to adopting and justifying the modelling methods used, and lack of clarity about the information on the cost estimation methods used.

The quality of data used in TA588² and NICE-Onasemnogene HST24-presymptomatic¹⁶ was highly appraised. Additionally, HST24-presymptomatic¹⁶ and Meijer et al. 2023²⁴⁸ were noted to maintain consistency in their methods, leading to a robust analysis. Zuluaga-Sanchez et al. 2019²⁵⁰ and Malone et al. 2019²⁵⁸ outperformed the other studies in terms of providing structural quality throughout the study and providing description and justification about the modelling methods and assumptions.

In conclusion, the methodological and structural uncertainties were addressed in most of the studies but showed inconsistencies in making assumptions about treatment effects, incorporation of data and addressing the uncertainties created in the analysis. The assessment of these studies was proposed to help improve the methodological quality and robustness of studies in future.

There were uncertainties around the methods used in identification, quality assessment and validation of data used in cost-effectiveness analysis in Khuntha et al. 2025.²⁴² Another section that was unclear was about the alternative assumption used around treatment effects and the lack of adequate discussion about the rationale of these assumptions in the analysis. In the model, it was unclear whether half-cycle correction was used. These are definite areas of improvement which were also observed in some studies in the original SLR.

14.15 Assessment of cost-effectiveness

14.15.1 Discussion

The original SLR, which included 20 studies, was updated to include the period post January 2024 to March 2025 and the results were updated accordingly. The studies that undertook cost-effectiveness analysis were included for assessing the different aspects of modelling in SMA. One new study was identified as relevant in the SLR update and presented the first economic evaluation of OA and risdiplam from a middle-income country in this SLR.²⁴²

Across all studies included in the original SLR and update, economic evaluations varied based on the target population considered, interventions and comparators included, outcomes, modelling methods, resource use and costs, health-state utility estimates, time horizons, analyses, assumptions and limitations, and patient and professional groups engagements. All of the studies were limited to patients with SMA types 1, 2 and/or 3, with some studies using subgroup analysis based on age and disease characteristics.² The interventions considered were risdiplam, nusinersen and/or onasemnogene abeparvovec, which were compared against the basic SoC available in the region. The cost-effectiveness was assessed using ICER that compared cost against unit of benefits (QALY or LYG) gained in all of these studies. Studies mostly adopted Markov models with health states defined by functional motor milestones and ventilation support, which were used to capture the SMA disease progression. There were marked differences in models in their time horizons, horizons, discount rates used for cost and utility estimates, and sources of utility values. The studies engaged with patients and experts in varying degrees when evaluating the treatments. The SLR thus provided critical and valuable insights to the different complexities that need to be addressed when considering SMA treatments.

14.15.1.1 Type of models including health states used

All the studies in consideration adopted the Markov models for the cost-effectiveness analysis. But there were some noticeable differences in terms of the included health states, structures, assumptions on disease progression, mortality and treatment efficacy. The definitions of the health states differed in terms of the disease progression and functional motor milestones observed in patients. In HST24,¹⁶ short-term and long-term models to capture different disease phases and milestones by using transitions between sitting, walking, and death. In terms of the models used, TA588¹⁷ used two separate Markov models to differentiate between infantile onset (SMA type 1) and later onset (SMA type 2/3) SMA. The elements under consideration among all the studies for modelling SMA treatments were assumptions on disease modification, treatment discontinuation, and survival were common factors influencing health

state selection and transitions, when deciding the health states and transitions between different health states. In Broekhoff et al. 2021²⁴⁵ the progression to specific health states was based on disease severity and treatment outcomes, thus reflecting the survival rates of different SMA types. All the studies had clear differences between health state selection and progression, which would indicate the need for better and transparent methodologies for accurate analysis of SMA treatments.

14.15.1.2 *Modelling long-term effects*

A very important consideration in SMA modelling is the long-term implications of treatments. But there are several limitations across these studies that reiterate the need for long term safety and efficacy data to fully capture the benefits of SMA treatments. Some of the bottle necks when it comes to modelling long-term impacts are treatment sustainability expressed in terms of motor function milestones and HRQoL. When it comes to lifetime projections, different patient characteristics, uncertainty in long-term effects and assumptions and varying definitions of motor milestones among the included studies were some of the factors that prove challenging in SMA analysis. For patients with different types of SMA, tailoring the economic evaluation is crucial in accurately reflecting the outcomes across different population groups with varying disease progression rates. There is an evidence gap around long-term follow-up data and real-world evidence, that could enhance the accuracy of evaluation and improve the decision-making on SMA treatments.

14.15.1.3 *Sources of utility estimates*

SMA is included in the category of rare diseases and hence it could be challenging to estimate robust utility values. In the absence of long-term data, studies conducted by NICE, ICER and CADTH indicate the complexities and variations in determining utility values for different health states in SMA patients. There is a broad lack of consensus among various studies about the best method to estimate the utility values.

The patient population concerned is paediatric population which makes it difficult to elicit utilities using measurement instruments designed for adults. There is a lack of validation of these values since the population is too young. TA588,² the CADTH-Nusinersen²⁵⁵ and CADTH-OA-2021²⁴⁴ outlines the challenges with robust utility values, use of generic patient-reported outcome measure to estimate health related quality of life and lack of long-term effectiveness data impacting the economic evaluations. These studies also point out that there was a lack of validity and reliability when it comes to clinical data. These challenges are compounded by a small sample population and absence of direct treatment comparison data, especially when it comes to nusinersen and risdiplam.

Another source of utility values observed were from clinical expert opinion, which is adopted in SMC studies. The NICE guidelines⁴⁰ stipulate that in the absence of reliable sources for measuring HRQoL in patients, the data could be obtained from caregivers rather than clinical experts. The health states in such situations should align closely with public opinion.

There is a need for continued research in exploring methods to collect robust data and transparent methods of reporting to create a consensus in techniques to improve the precision and reliability of treatments in rare diseases like SMA.

14.15.1.4 *Sources of resource use and costs*

The sources of resource use and cost used differed based on the region of the study. For example, TA588² and TA755³ used data specific to the UK. CADTH-Nusinersen²⁵³ and

CADTH-Risdiplam²⁵⁵ appraisal resource use and costs were obtained from studies undertaken in Germany and Canada, respectively. This would result in variation in the resource use and cost estimation in the model, leading to the results being not fit to be compared.

Another method adopted was introducing age-adjustment in estimating costs, which would give insights about the nuances associated with financial burden of SMA treatments on patients at different stages of their life.

The different assumptions made across various studies did impact the cost estimates. This resulted in discrepancies that reflected in the cost-effectiveness results across various studies. Some of the factors that influenced the cost estimates were assumptions around long-term treatment effects, disease progression, differences in discontinuation rates and assumptions around additional costs incurred to patients.

Another aspect that influenced the resource use and cost estimates were varying definitions of BSC or standard of care. When new treatments options are added to BSC or standard care, it impacts the cost-effectiveness estimation resulting from variation in baseline estimates. (TA588² and CADTH-Risdiplam²⁵⁵)

Additionally, there is lack of clinical data from direct comparison of treatment efficacy between various treatments and standard of care. There are discrepancies in data sources, methodologies and assumptions around estimation of cost and resource use data.

In short, the factors under consideration for estimating resource use and cost in SMA treatments are data sources, age-adjusted cost estimates, assumptions around resource use and treatment modelling, different definitions of BSC or standard of care, and other complexities and heterogeneity around SMA treatment modelling assumptions, that makes the comparison of estimates among different studies difficult.

14.16 Conclusion

All the included studies from the SLR undertook economic evaluation of SMA treatments. The studies varied based on the patient population, interventions and comparators, outcome measures, modelling methods adopted, resource use and costs, health-state utility estimates, time horizons, analyses, assumptions and limitations, and patient and professional engagements. SMA types 1, 2 and/or 3 were considered in most of the studies, with some using subgroup analysis based on age and disease characteristics.

There was a consensus in the type of model adopted for cost-effectiveness evaluation, with the studies using Markov models for estimating the SMA treatment effectiveness. There was a need for generating robust and reliable data on long-term follow-up and real-world evidence on treatment efficacy that could enhance the accuracy of evaluation and improve the decision-making on SMA treatments. There were significant variations in sources and methods used for utility estimates among different studies, due to a lack of consensus around the best source and methods that could be used to elicit the utility estimates. The resource use quantification and subsequent cost estimation was influenced by variations in data sources, age-adjusted cost estimates, assumptions in treatment modelling, definitions of BSC or standard of care, and other complexities and heterogeneity around SMA treatment modelling assumptions, resulting in the cost-effectiveness results across the studies not fit for comparison. It would be difficult to draw conclusions to inform SMA treatment modelling choices from the results of the SLR. But these studies could be used to analyse the impact of different data sources, methods

and assumptions in modelling SMA treatments. The assessment of cost-effectiveness SLR results indicate a need for robust and reliable data on treatment effectiveness, real-world evidence generation of utility estimates and consensus in adopting resource use and estimating costs for SMA treatment evaluation.

15 EAG cost-effectiveness analysis results

This section presents the results from the independent assessment of cost-effectiveness of the disease modifying therapies conducted by the EAG. These results should be read in the context of the qualitative analysis exploring experiences of those living with SMA, their carers and wider network of family and friends, as well as their experiences of treatment. The qualitative analyses related specifically to the cost effectiveness analyses can be found in Section 1.1.

Based on the results from the EAG base-case analyses presented independently for nusinersen and risdiplam based exclusively on patient quality of life, the EAG assessed the eligibility across each patient population to the severity modifier criteria. Table 106 reports the most appropriate severity modifier by treatment based on the QALY estimates in each economic model.

Table 106: Severity modifier eligibility based on the EAG base-case analyses for the economic models in each company

Population	Expected QALYs	BSC QALYs	Absolute shortfall	Proportional Shortfall	Eligible severity modifier
Biogen - nusinersen					
Presymptomatic	24.89				1.2
Type 1	24.87				1.7
Type 2&3	24.55				1.2
Roche - risdiplam					
Presymptomatic	24.87				1.7
Type 1	24.87				1.7
Type 2&3	24.02				1.2
Abbreviations: QALY = quality adjusted life year; BSC = best supportive care					

15.1 Nusinersen – using Biogen model

15.1.1 Presymptomatic

This section presents the EAG results for the presymptomatic population. The EAG's definition of base-case cost-effectiveness analysis for presymptomatic population is presented in Section 12.2.1.

15.1.1.1 Deterministic base-case analysis

The EAG's base-case analysis (without incorporating the severity modifier) show that nusinersen would be a less costly and more effective (dominant)_treatment over BSC in presymptomatic population (Table 107). Even after applying the severity modifier, nusinersen remained dominant treatment.

Table 107: Deterministic base-case results for the presymptomatic population (using nusinersen PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	ICER (£/QALY)-with

								severity modifier
Nusinersen	██████	20.65	████	-	-	-	-	-
BSC	██████	19.84	████	██████	0.81	████	Dominant	Dominant
Abbreviations: BSC = Best Supportive Care, ICER = Incremental Cost-Effectiveness Ratio, LYG = Life-Year Gained, QALY = Quality Adjusted Life Years, NHB = Net Health Benefits.								

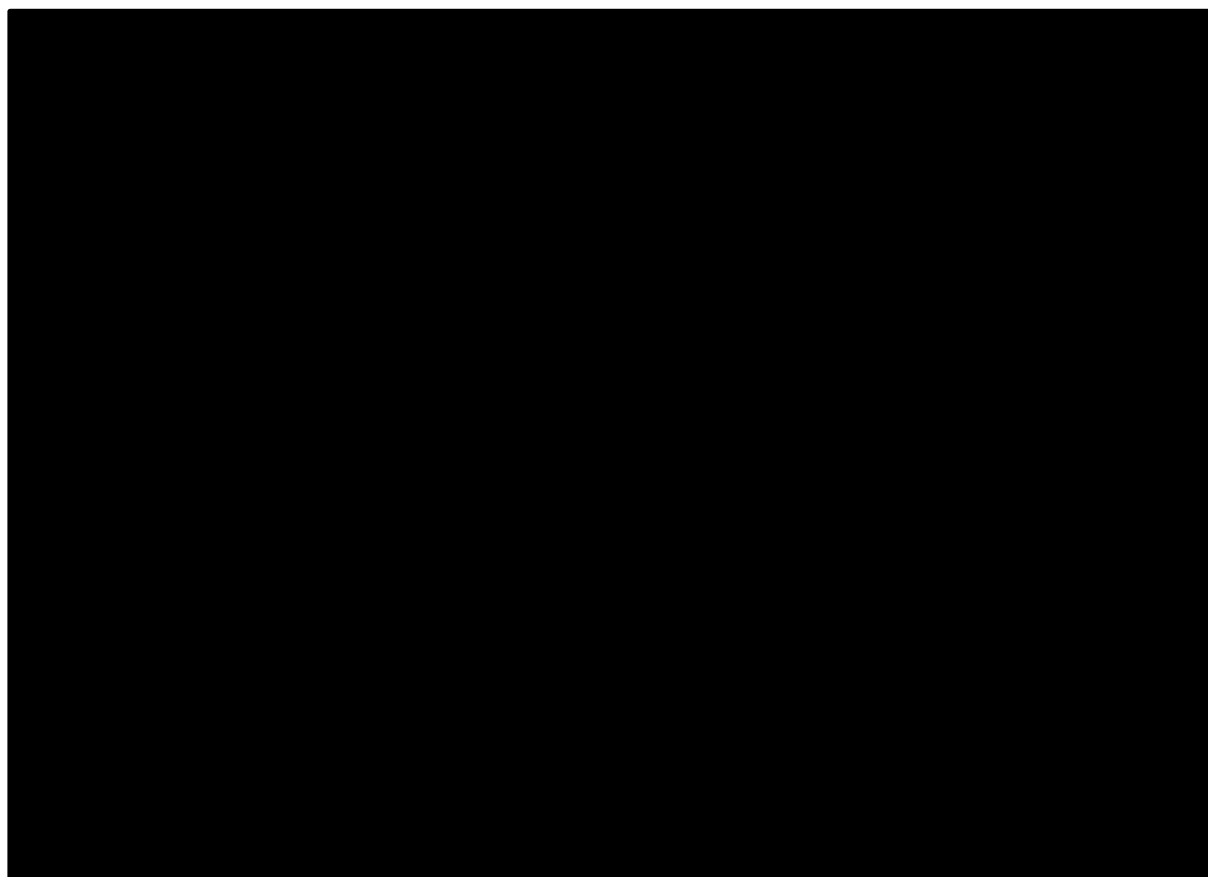
15.1.1.2 Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis (PSA), the base-case deterministic results remained mostly stable, where nusinersen was still a dominant intervention over BSC in the treatment of presymptomatic population (Table 108). The cost-effectiveness plane shows that a majority of cost-effectiveness simulations run had ██████████ for nusinersen when compared with BSC (Figure 34). The probability of nusinersen being cost-effective over BSC was █████ (Figure 35).

Table 108: Probabilistic results for the presymptomatic population (using nusinersen PAS price)

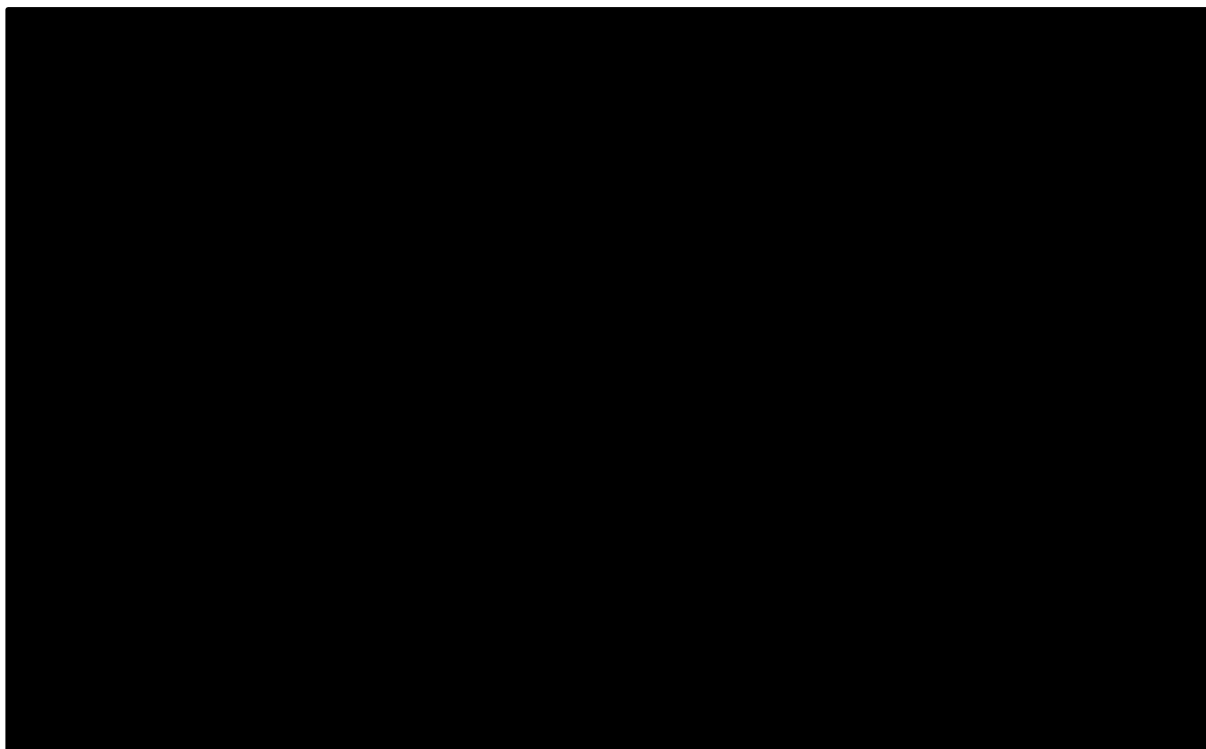
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Nusinersen	██████ ██████	20.69 (20.34 to 21)	██████ ██████	-	-	-	-
BSC	██████ ██████ ██████	19.85 (19.50 to 20.15)	██████ ██████	██████ ██████ ██████	0.84 (0.58 to 1.10)	██████ ██████	Dominant
Probability cost-effective at a 30k willingness to pay value							████
Abbreviations: BSC: Best Supportive Care, ICER: Incremental Cost-Effectiveness Ratio, LYG: Life-Year Gained, QALY: Quality Adjusted Life Years, NHB: Net Health Benefits							

Figure 34: Cost-effectiveness plot showing cost-effectiveness of nusinersen vs BSC (presymptomatic)



Abbreviations: BSC = best supportive care; GBP = British pounds; QALY = quality-adjusted life year

Figure 35: Cost-effectiveness acceptability curve for nusinersen vs BSC

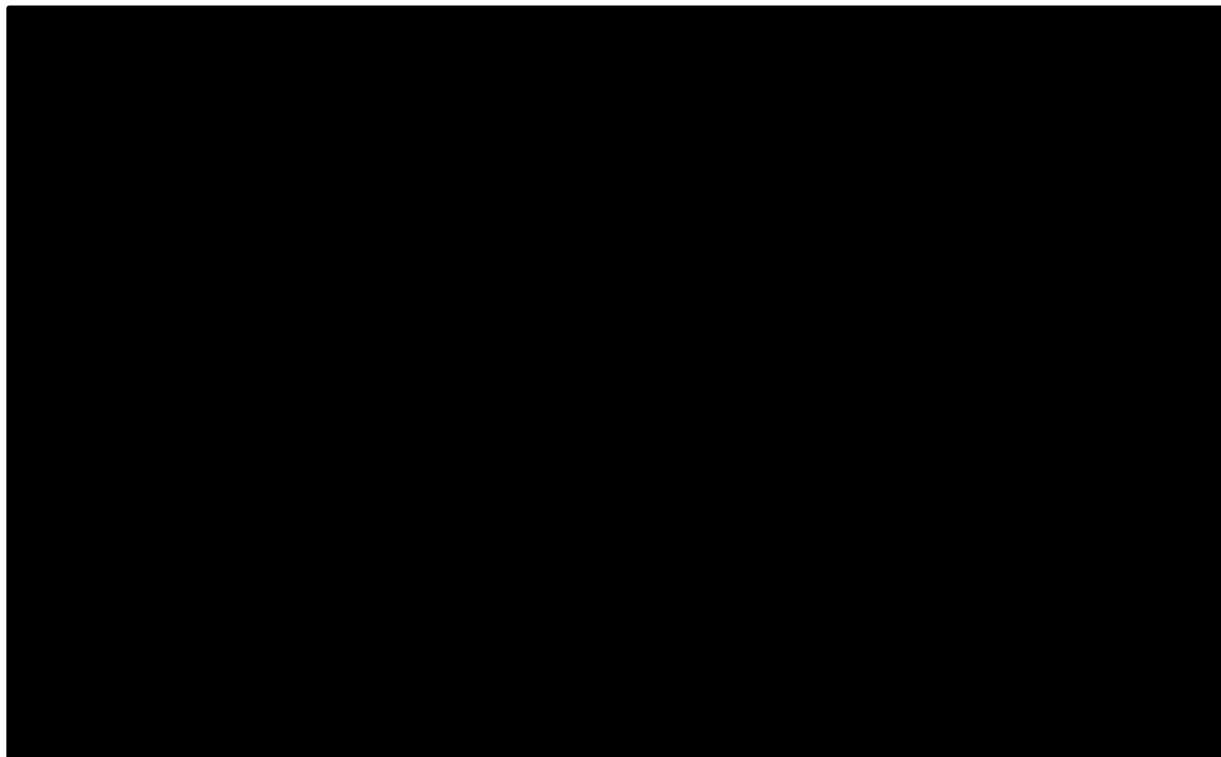


Abbreviations: BSC = best supportive care; GBP = British pounds; QALY = quality-adjusted life year; WTP = willingness to pay

15.1.1.3 One-way sensitivity analysis

The one-way sensitivity analysis suggested the health state costs (not sitting, sitting without support, permanent ventilation) followed by health state utilities had highest impact on the ICER (Figure 36). However, nusinersen [REDACTED] in all the 9 parameter changes where impact on ICER was observed.

Figure 36: Deterministic one-way sensitivity analysis for the comparison between nusinersen and BSC (presymptomatic, using the PAS price for nusinersen)



Abbreviations: BSC = best supportive care; PAS = Patient Access Scheme

15.1.1.4 Scenario analyses

The scenario analyses conducted by the EAG, to assess the impact of parameter changes to baseline cost-effectiveness results, are summarised in Table 109. A subgroup analysis for each of the population with SMN2 and SMN3 copies was also conducted. In addition, the EAG also assessed the cost-effectiveness of nusinersen vs OA (Table 109).

With the nusinersen PAS price, the cost-effectiveness results were [REDACTED] in all the scenarios including the sub-groups of SMN2 and SMN3 populations, except in the scenario when the healthcare resource utilisation costs were sourced from TA588²/TA755³, where the [REDACTED] the £30,000 willingness to pay threshold set by NICE. Assuming £0 price for nusinersen resulted in [REDACTED] List price analyses have been included to aid transparency.

In the scenarios, where nusinersen was compared with OA (Table 110), the cost-effectiveness results [REDACTED] when nusinersen PAS price was used. These results were based on list price for OA. However, these results comparing nusinersen against OA needs to be interpreted with caution, because of the assumptions of clinical equivalence (all parameters assumed equal with nusinersen apart from the price of the therapy) or non-equivalence (based on differences in state occupancy informed by poor evidence from an unanchored MAIC from SPR1NT data³¹). In the EAG model, discontinuations from nusinersen (as modelled in the company submission) to BSC were kept unchanged. In contrast, no discontinuations from OA were considered practical. Therefore, driven by these discontinuation assumptions, there remains a QALY difference between nusinersen and OA in the results, even when equivalence in state occupancy is assumed.

Table 109: Scenario analyses for cost-effectiveness of nusinersen vs BSC in presymptomatic population

Scenario	Incremental costs (£)	Incremental Life Years	Incremental QALYs	ICER (£/QALY)	NHB at £30,000/QALY
With nusinersen PAS price					
Including carer utilities from Lo et al. ⁷¹	[REDACTED]	0.81	[REDACTED]	Dominant	[REDACTED]
Utilities sourced from TA755	[REDACTED]	0.81	[REDACTED]	Dominant	[REDACTED]
Health state costs sourced from TA588 and TA755	[REDACTED]	0.81	[REDACTED]	[REDACTED]	[REDACTED]
Sub-group (2 copies)	[REDACTED]	1.27	[REDACTED]	Dominant	[REDACTED]
Sub-group (3 copies)	[REDACTED]	0.38	[REDACTED]	[REDACTED]	[REDACTED]
£0 nusinersen price	[REDACTED]	0.81	[REDACTED]	Dominant	[REDACTED]
With nusinersen list price					

Scenario	Incremental costs (£)	Incremental Life Years	Incremental QALYs	ICER (£/QALY)	NHB at £30,000/QALY
Base-case	██████	0.81	████	██████	████
Including carer utilities	██████	0.81	████	£226,607	████
Utilities sourced from TA755	██████	0.81	████	£274,407	████
Health state costs sourced from TA588 and TA755	██████	0.81	████	£387,291	████
Sub-group (2 copies)	██████	1.27	████	£250,886	████
Sub-group (3 copies)	██████	0.38	████	£442,724	████
Abbreviations: BSC: Best Supportive Care, ICER: Incremental Cost-Effectiveness Ratio, LYG: Life-Year Gained, QALY: Quality Adjusted Life Years, NHB: Net Health Benefits.					

Table 110: Deterministic cost-effectiveness analysis of nusinersen vs OA

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/ QALY)
Scenario: Nusinersen vs OA (using PAS price for nusinersen)							
Nusinersen	██████	20.65	████	████	-	████	████
OA (equivalence assumed in state occupancy)	██████	24.25	████	██████	-3.60	████	████████████████ ████████████████ ████████████████ ████████████████
OA (no equivalence assumed in state occupancy)	██████	24.26	████	██████	-3.61	████	████████████████ ████████████████ ████████████████ ████████████████
Scenario: Nusinersen vs OA (using list price for nusinersen)							
Nusinersen	██████	20.65	████	████	=	████	-
OA (equivalence assumed in state occupancy)	██████	24.25	████	██████	-3.60	████	Dominated
OA (no equivalence assumed in state occupancy)	██████	24.26	████	██████	-3.61	████	Dominated
Dominated: More costly, less effective							
Abbreviations: BSC: Best Supportive Care, ICER: Incremental Cost-Effectiveness Ratio, LYG: Life-Year Gained, QALY: Quality Adjusted Life Years, NHB: Net Health Benefits.							

15.1.2 Type 1

This section presents the EAG results for the type 1 SMA population. The EAG's definition of base-case cost-effectiveness analysis for type 1 SMA population is presented in Section 8.2.1.

15.1.2.1 Deterministic base-case analysis

The EAG's base-case analysis (without incorporating the severity modifier) findings show that [REDACTED] than the £30,000 willingness to pay threshold, and nusinersen would [REDACTED] intervention in the treatment of type1 SMA population (Table 111). Applying the severity modifier lowered the ICER [REDACTED] but it remained [REDACTED] NICE's willingness to pay threshold, therefore nusinersen was [REDACTED].

Table 111: Deterministic base-case results for the type 1 population (using nusinersen PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	ICER (£/QALY)-with severity modifier
Nusinersen	[REDACTED]	6.81	[REDACTED]	-	-	-	-	-
BSC	[REDACTED]	2.91	[REDACTED]	[REDACTED]	3.90	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: BSC: Best Supportive Care, ICER: Incremental Cost-Effectiveness Ratio, LYG: Life-Year Gained, QALY: Quality Adjusted Life Years, NHB: Net Health Benefits.

15.1.2.2 Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis (PSA), the base-case deterministic results remained mostly stable, where nusinersen was [REDACTED] compared with BSC (Table 112).

The cost-effectiveness plane (Figure 37) shows that a majority of cost-effectiveness simulations run [REDACTED] QALY gains for nusinersen when compared with BSC. The probability of nusinersen being cost-effective over BSC was [REDACTED] (Figure 38).

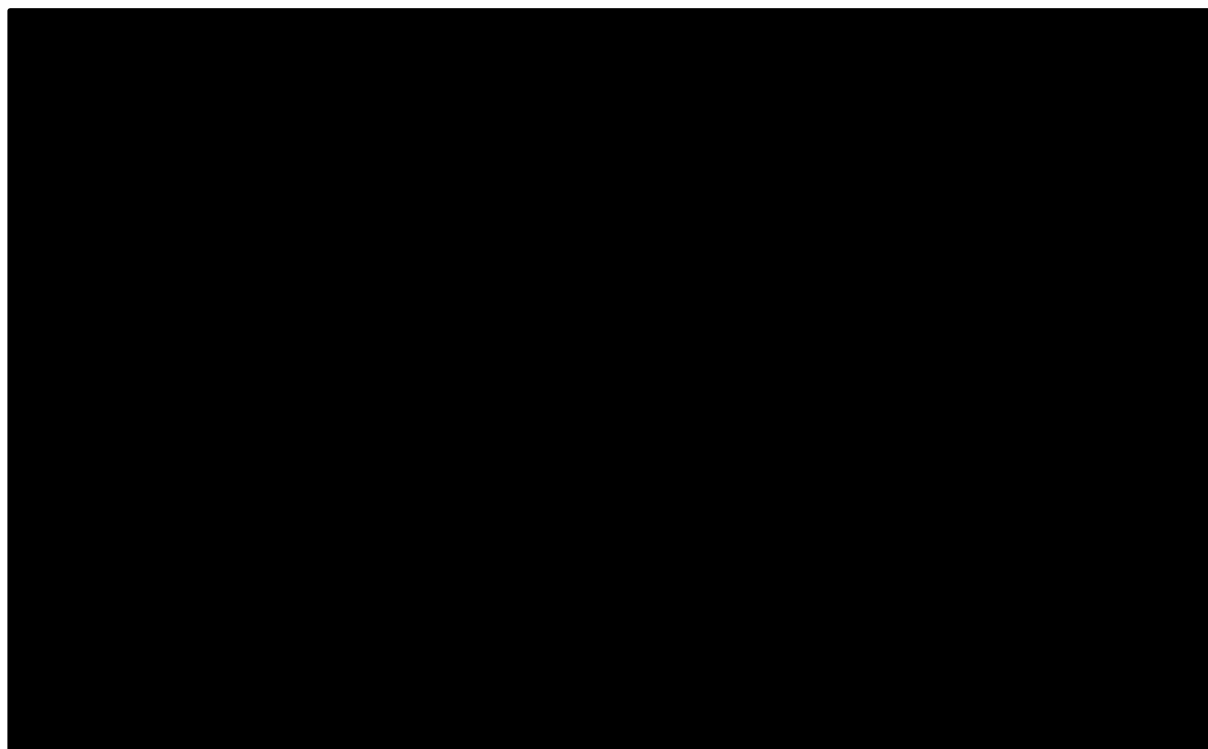
Table 112: Probabilistic results for the type 1 population (using nusinersen PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Nusinersen	[REDACTED]	6.87 (5.70 to 8.36)	[REDACTED]	-	-	-	-
BSC	[REDACTED]	3.05 (1.57 to 5.21)	[REDACTED]	[REDACTED]	3.82 (2.72 to 4.82)	[REDACTED]	[REDACTED]

Probability cost-effective at a 30k willingness to pay value [REDACTED]

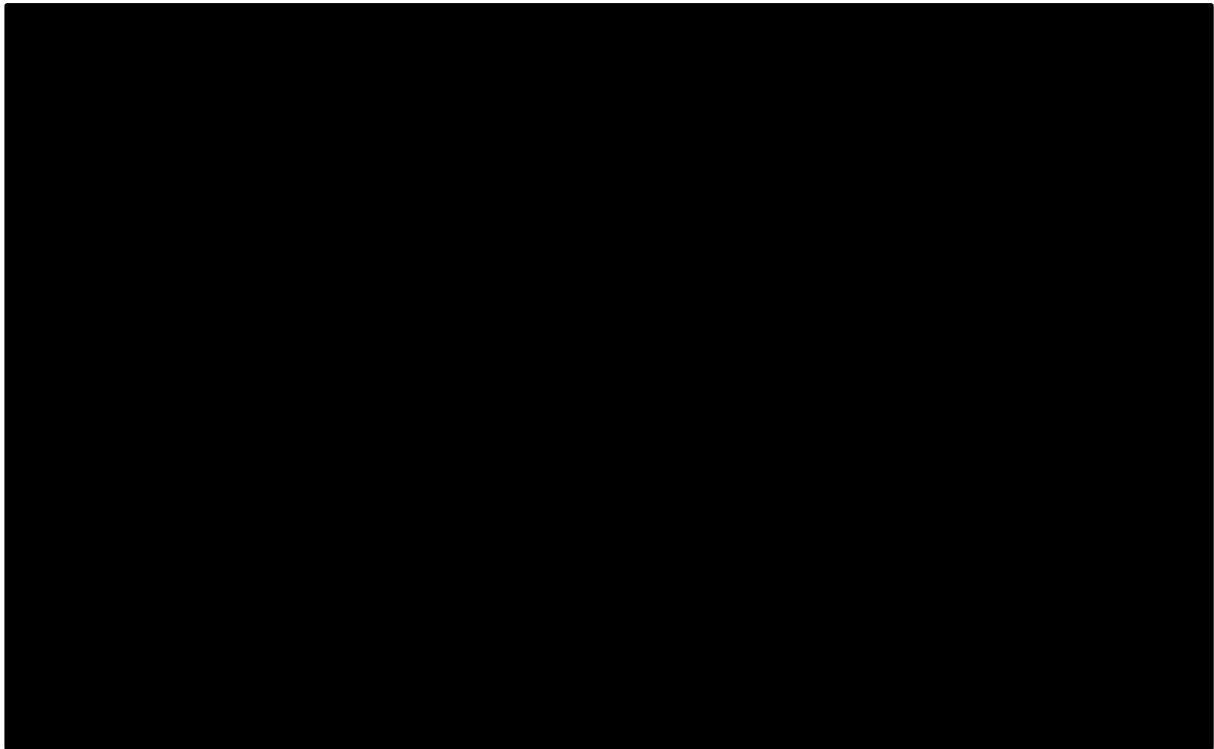
Abbreviations: BSC: Best Supportive Care, ICER: Incremental Cost-Effectiveness Ratio, LYG: Life-Year Gained, QALY: Quality Adjusted Life Years, NHB: Net Health Benefits.

Figure 37: Cost-effectiveness plot showing cost-effectiveness of nusinersen vs BSC (type 1)



Abbreviations: BSC = best supportive care; GBP = British pounds; QALY = quality-adjusted life year

Figure 38: Cost-effectiveness acceptability curve for nusinersen vs BSC (type 1)

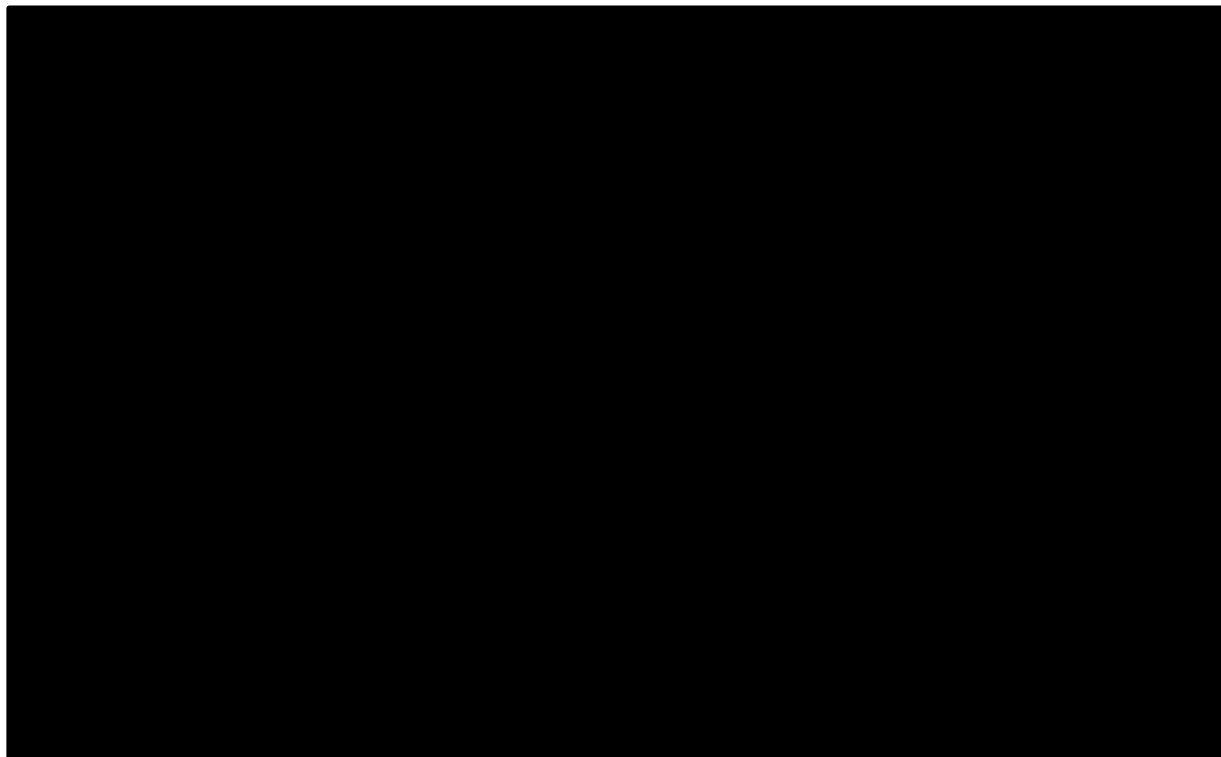


Abbreviations: BSC = best supportive care; GBP = British pounds; QALY = quality-adjusted life year; WTP = willingness to pay

15.1.2.3 One-way sensitivity analysis

The EAG one-way sensitivity analyses showed that changing the health state utilities by +/- 20% had a highest impact on the ICER, followed by health state costs for permanent ventilation, not sitting, and sitting without support respectively (Figure 39). Per-cycle discontinuation rates for standing with support had the least impact followed by standing with support.

Figure 39: Deterministic one-way sensitivity analysis for the comparison between nusinersen and BSC (type 1, using the PAS price for nusinersen)



Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; PAS = Patient Access Scheme; QALY = quality-adjusted life year

15.1.2.4 Scenario analyses

The scenario analyses conducted by the EAG, to assess the impact of parameter changes to baseline cost-effectiveness results, are summarised in Table 113. In addition, the EAG also assessed the cost-effectiveness of nusinersen vs OA (Table 114). The list price was used for OA.

With the nusinersen PAS price or list price, the cost-effectiveness results were not in favour of nusinersen in all the scenarios because the ICER was well above the £30,000 willingness to pay threshold set by NICE. In addition, [REDACTED].

In the scenarios, where nusinersen was compared with OA (Table 114), the cost-effectiveness results were not in favour of nusinersen with nusinersen being less costly and less effective when either of the nusinersen PAS price or list price was used. However, these results comparing nusinersen against OA need to be interpreted with caution, because of the assumptions of clinical equivalence (all parameters assumed equal with nusinersen apart from the price of the therapy) or non-equivalence (based on differences in state occupancy informed by poor evidence from an unanchored MAIC from STRIVE data³¹). In the EAG model, discontinuations from nusinersen (as modelled in the company submission) to BSC were kept unchanged. In contrast, no discontinuations from OA were considered practical. Therefore, driven by these discontinuation assumptions, there remains a QALY difference between nusinersen and OA in the results, even when equivalence in state occupancy is assumed.

Table 113: Scenario analyses for cost-effectiveness of nusinersen vs BSC in type 1 population

Scenario	Incremental costs (£)	Incremental Life Years	Incremental QALYs	ICER (£/QALY)	NHB at £30,000/QALY
With nusinersen PAS price					
Including carer utilities Lo et al ⁷¹	[REDACTED]	3.90	[REDACTED]	[REDACTED]	[REDACTED]
Utilities sourced from TA755	[REDACTED]	3.90	[REDACTED]	[REDACTED]	[REDACTED]
Health state costs sourced from TA588 and TA755	[REDACTED]	3.90	[REDACTED]	[REDACTED]	[REDACTED]
£0 nusinersen price	[REDACTED]	3.90	[REDACTED]	[REDACTED]	[REDACTED]
With nusinersen list price					
Base-case	[REDACTED]	3.90	[REDACTED]	£534,405	[REDACTED]

Scenario	Incremental costs (£)	Incremental Life Years	Incremental QALYs	ICER (£/QALY)	NHB at £30,000/QALY
Including carer utilities	██████	3.90	██	£522,281	████
Utilities sourced from TA755	██████	3.90	██	£879,292	██
Health state costs sourced from TA588 and TA755	██████	3.90	██	£564,976	████
Abbreviations: BSC: Best Supportive Care, ICER: Incremental Cost-Effectiveness Ratio, LYG: Life-Year Gained, QALY: Quality Adjusted Life Years, NHB: Net Health Benefits.					

Table 114: Deterministic cost-effectiveness analysis of nusinersen vs OA

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Scenario: Nusinersen vs OA (with PAS price for nusinersen)							
Nusinersen	██████	6.81	██	-	-	-	-
OA (equivalence assumed in state occupancy)	██████	15.68	██	██████	-8.87	██	████████████████████ ████████████████████ ████████████████████
OA (no equivalence assumed in state occupancy)	██████	15.68	██	██████	-8.87	██	████████████████████ ████████████████████ ████████████████████
Scenario: Nusinersen vs OA (with list price for nusinersen)							
Nusinersen	██████	6.81	██	-	-	-	-
OA (equivalence assumed in state occupancy)	██████	15.68	██	██████	-8.87	██	Less costly, less effective (ICER for OA vs Nusinersen= £307,697)
OA (no equivalence assumed in state occupancy)	██████	15.68	██	██████	-8.87	██	Less costly, less effective (ICER for OA vs Nusinersen= £305,312)
Abbreviations: BSC: Best Supportive Care, ICER: Incremental Cost-Effectiveness Ratio, LYG: Life-Year Gained, QALY: Quality Adjusted Life Years, NHB: Net Health Benefits.							

15.1.3 Type 2/3

This section presents the EAG results for type 2/3 SMA. The EAG's definition of base-case cost-effectiveness analysis for type 2/3 SMA population is presented in Section 12.2.1.3.

15.1.3.1 Deterministic base-case analysis

The EAG's base-case analysis (without incorporating the severity modifier) findings show that ICER [REDACTED] than the £30,000 willingness to pay threshold, and nusinersen [REDACTED] intervention in the treatment of type 2/3 SMA population (Table 115). Applying the severity modifier lowered the ICER [REDACTED] but it remained [REDACTED] NICE's willingness to pay threshold, therefore nusinersen was [REDACTED].

Table 115: Deterministic base-case results for the type 2/3 population (using nusinersen PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	ICER (£/QALY)-with severity modifier
Nusinersen	[REDACTED]	23.08	[REDACTED]	-	-	-	-	-
BSC	[REDACTED]	22.85	[REDACTED]	[REDACTED]	0.23	[REDACTED]	[REDACTED]	[REDACTED]
Abbreviations: BSC: Best Supportive Care, ICER: Incremental Cost-Effectiveness Ratio, LYG: Life-Year Gained, QALY: Quality Adjusted Life Years, NHB: Net Health Benefits; PAS = Patient Access Scheme								

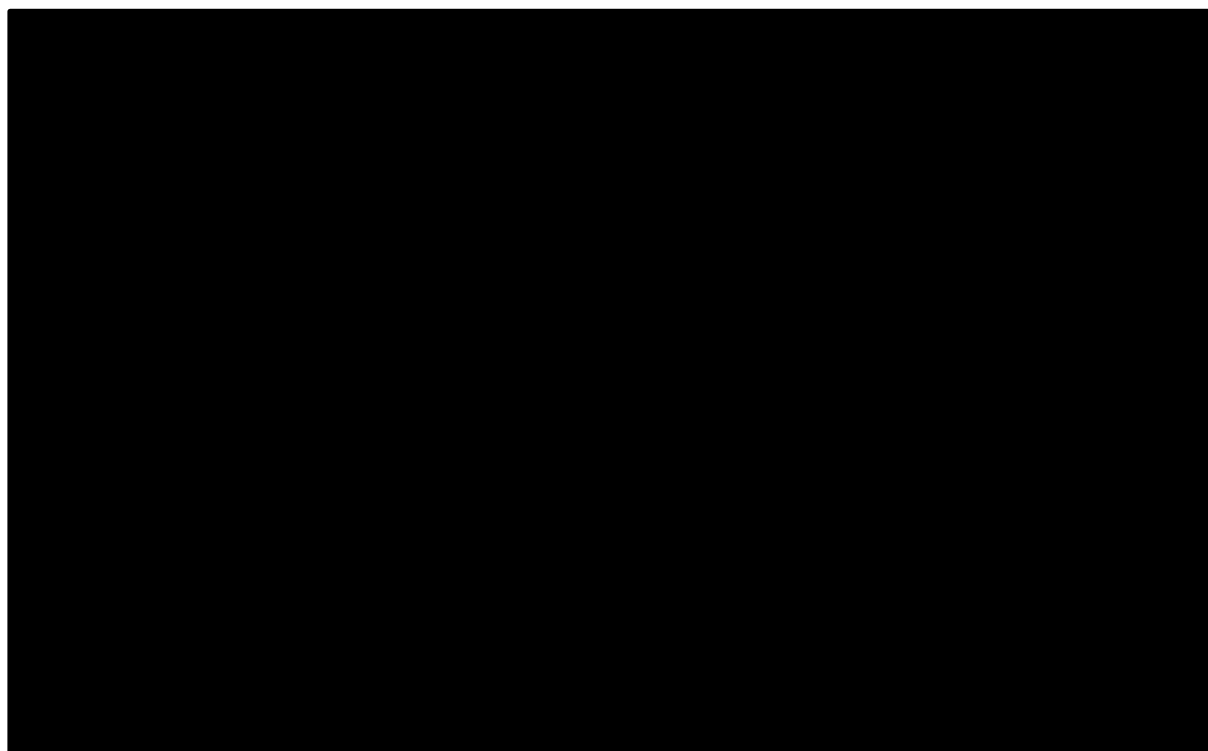
15.1.3.2 Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis (PSA), the base-case deterministic results remained mostly stable, where [REDACTED] compared with BSC (Table 116). The cost-effectiveness plane (Figure 40) shows that all of the cost-effectiveness simulations run [REDACTED] for nusinersen when compared with BSC. The probability that nusinersen being cost-effective over BSC was [REDACTED] (Figure 41).

Table 116: Probabilistic results for the type 2/3 population (using nusinersen PAS price)

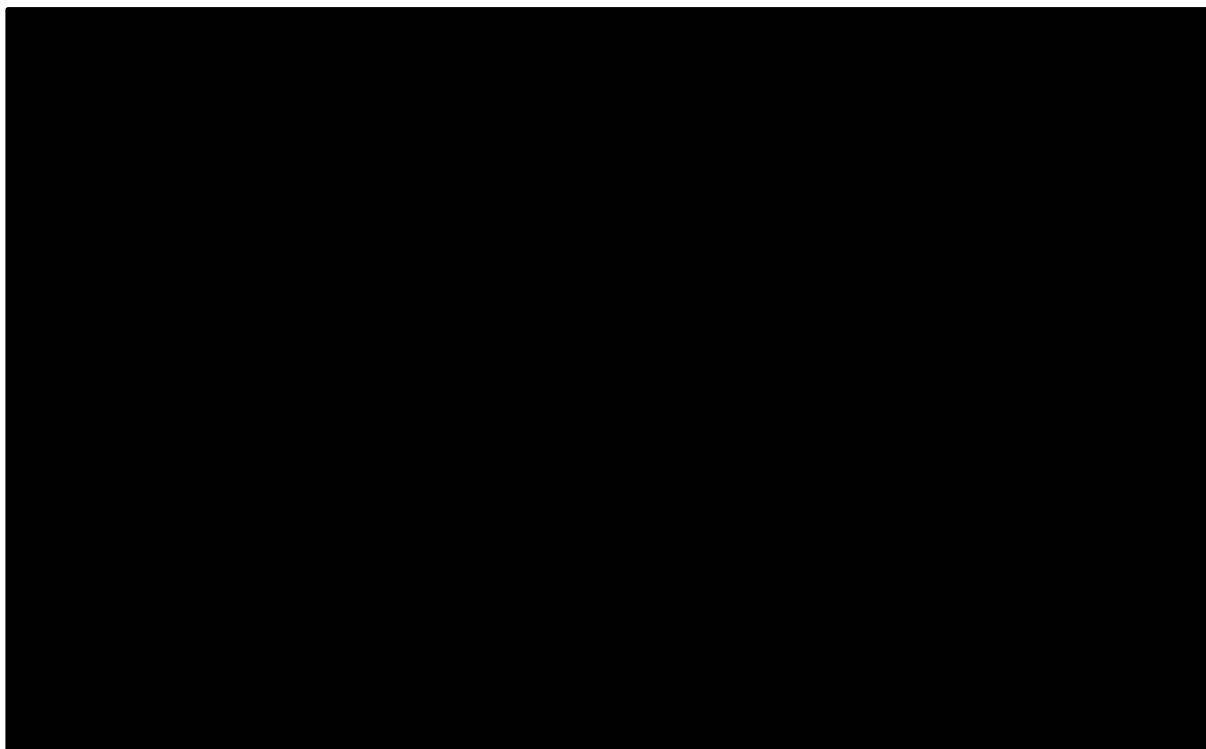
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Nusinersen	[REDACTED] [REDACTED] [REDACTED] [REDACTED]	23.08 (23.03 to 23.14)	[REDACTED] [REDACTED] [REDACTED]	-	-	-	-
BSC	[REDACTED] [REDACTED] [REDACTED] [REDACTED]	22.85 (22.80 to 22.90)	[REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]	0.23 (0.19 to 0.28)	[REDACTED] [REDACTED]	[REDACTED]
Probability cost-effective at a 30k willingness to pay value							[REDACTED]
Abbreviations: BSC: Best Supportive Care, ICER: Incremental Cost-Effectiveness Ratio, LYG: Life-Year Gained, QALY: Quality Adjusted Life Years, NHB: Net Health Benefits.							

Figure 40: Cost-effectiveness plot showing cost-effectiveness of nusinersen vs BSC (type 2/3)



Abbreviations: BSC = best supportive care; GBP = British pounds; QALY = quality-adjusted life year

Figure 41: Cost-effectiveness acceptability curve for nusinersen vs BSC (type 2/3)

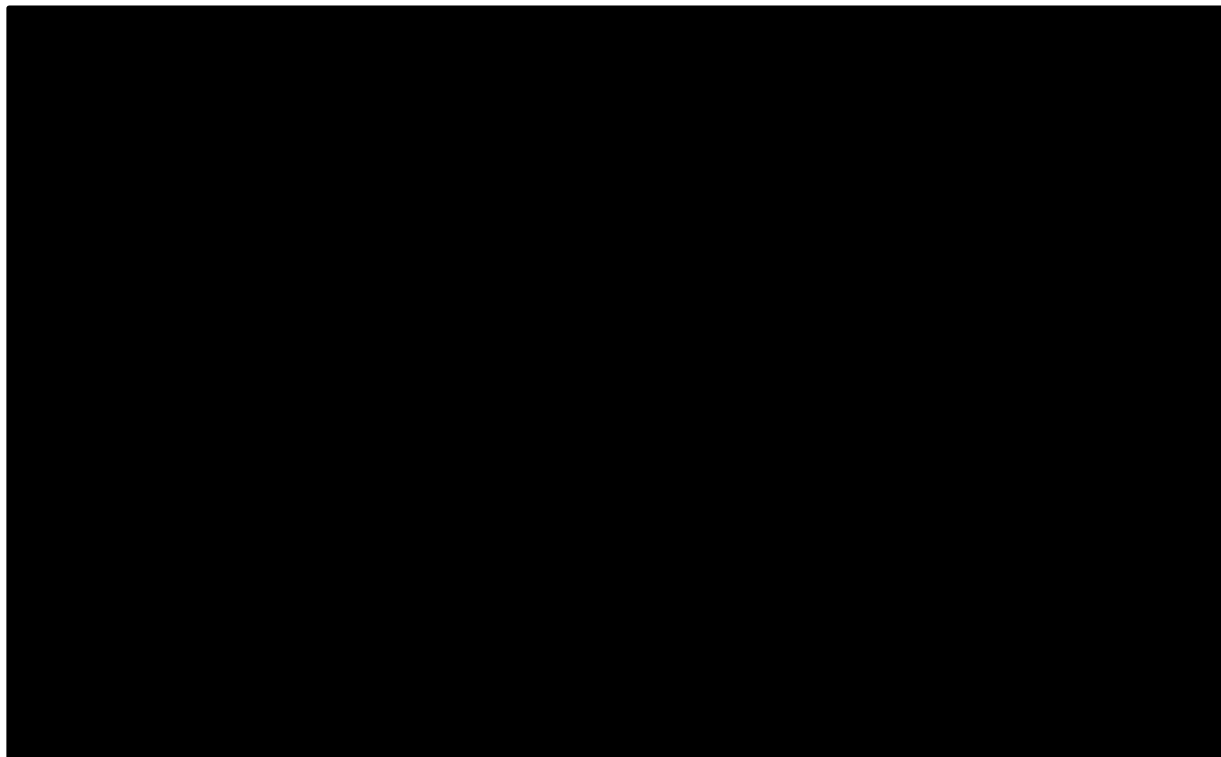


Abbreviations: BSC = best supportive care; GBP = British pounds; QALY = quality-adjusted life year; WTP = willingness to pay

15.1.3.3 One-way sensitivity analysis

The EAG's one-way sensitivity analyses (Figure 42) showed that changing health state costs for "sitting without support", followed by changes in annual state utilities, and health state costs for "not sitting" and "sitting without support" had the highest impact on the base case results. Per cycle discontinuation in "not sitting" had the least impact, followed by health state costs of walking independently.

Figure 42: Deterministic one-way sensitivity analysis for the comparison between nusinersen and BSC (type 2/3, using the PAS price for nusinersen)



Abbreviations: BSC = best supportive care; GBP = British pounds; ICER = incremental cost-effectiveness ratio; PAS = Patient Access Scheme; QALY = quality-adjusted life year

15.1.3.4 Scenario analyses

The scenario analyses conducted by the EAG, to assess the impact of parameter changes to baseline cost-effectiveness results, is summarised in (Table 117). With the nusinersen [REDACTED] in all the scenarios because the ICER was [REDACTED] willingness to pay threshold set by NICE. However, [REDACTED]

Table 117: Scenario analyses for cost-effectiveness of nusinersen vs BSC in type 2/3 population

Scenario	Incremental costs (£)	Incremental Life Years	Incremental QALYs	ICER (£/QALY)	NHB at £30,000/QALY
With nusinersen PAS price					
Including carer utilities from Lo et al. ⁷¹	[REDACTED]	0.23	[REDACTED]	[REDACTED]	[REDACTED]
Utilities sourced from TA755	[REDACTED]	0.23	[REDACTED]	[REDACTED]	[REDACTED]
Health state costs sourced from TA588 and TA755	[REDACTED]	0.23	[REDACTED]	[REDACTED]	[REDACTED]
Utilities sourced from Roche base-case i.e. from Lloyd 2019	[REDACTED]	0.23	[REDACTED]	[REDACTED]	[REDACTED]
Utilities sourced from Roche SUNFISH trial	[REDACTED]	0.23	[REDACTED]	[REDACTED]	[REDACTED]
With additional impact of bulbar dysfunction	[REDACTED]	0.23	[REDACTED]	[REDACTED]	[REDACTED]
Subgroup (type 2 SMA)	[REDACTED]	0.14	[REDACTED]	[REDACTED]	[REDACTED]
Subgroup (type 3 SMA)	[REDACTED]	0.13	[REDACTED]	[REDACTED]	[REDACTED]
£0 nusinersen price	[REDACTED]	0.23	[REDACTED]	[REDACTED]	[REDACTED]
With nusinersen list price					

Scenario	Incremental costs (£)	Incremental Life Years	Incremental QALYs	ICER (£/QALY)	NHB at £30,000/QALY
Base-case	██████	0.23	██	£781,225	████
Including carer utilities	██████	0.23	██	£557,210	████
Utilities sourced from TA755	██████	0.23	██	£581,533	████
Health state costs sourced from TA588 and TA755	██████	0.23	██	£824,916	████
Utilities sourced from Roche base-case i.e. from Lloyd 2019	██████	0.23	██	£651,232	████
Utilities sourced from Roche SUNFISH trial	██████	0.23	██	£1,330,593	████
With additional impact of bulbar dysfunction	██████	0.23	██	£782,332	████
Subgroup (type 2 SMA)	██████	0.14	██	£1,365,398	████
Subgroup (type 3 SMA)	██████	0.13	██	£1,232,287	████
Abbreviations: BSC: Best Supportive Care, ICER: Incremental Cost-Effectiveness Ratio, LYG: Life-Year Gained, PAS = Patient Access Scheme; QALY: Quality Adjusted Life Years, NHB: Net Health Benefits.					

15.2 Risdiplam - using Roche model

15.2.1 Presymptomatic

15.2.1.1 Deterministic base-case analysis

The base-case analysis for the presymptomatic population comparing risdiplam with BSC, focusing on patient HRQoL, including the PAS discount for risdiplam, showed that risdiplam [REDACTED] NICE's £20,000/QALY willingness to pay threshold. Applying a severity modifier of 1.7 led to a reduction of the risdiplam ICER to [REDACTED] QALY.

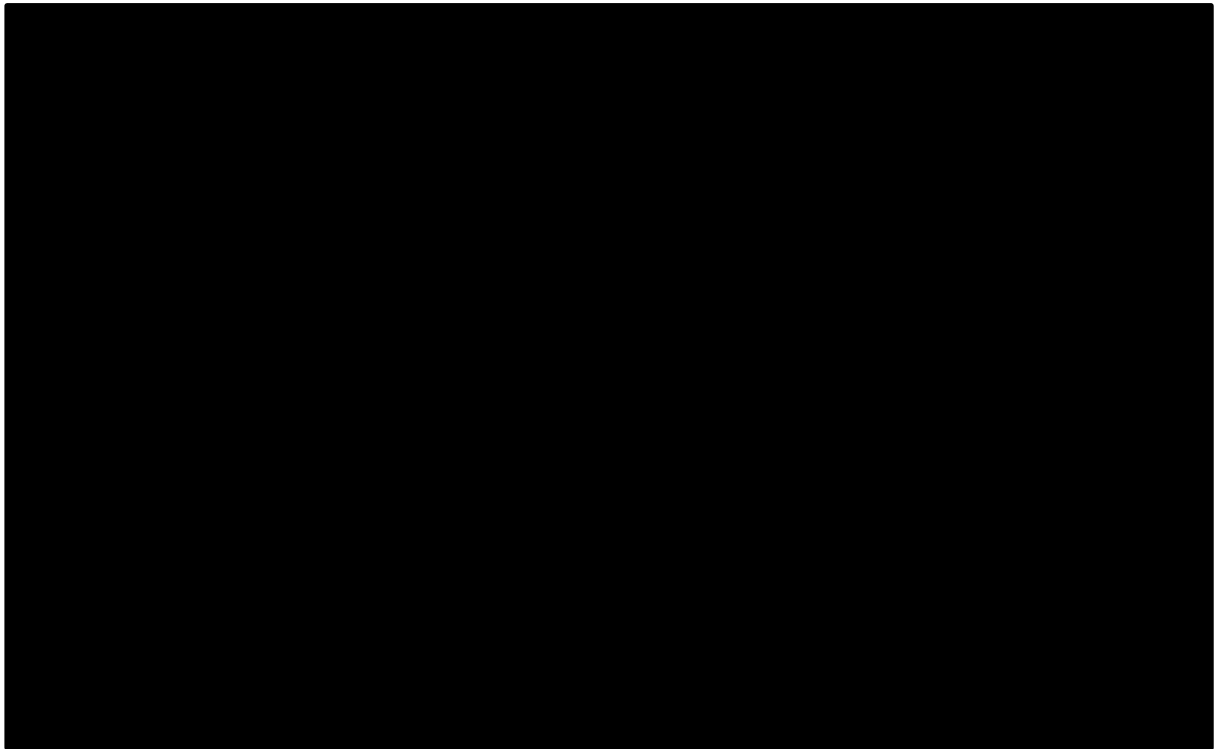
Probabilistic results showed that risdiplam was [REDACTED] [REDACTED] [REDACTED] and [REDACTED] [REDACTED] with an ICER of [REDACTED]. Applying a severity modifier of 1.7 led to an ICER of [REDACTED]. This showed a substantial uncertainty in the incremental costs of risdiplam compared to BSC. Table 119 reports deterministic and probabilistic results (Table 118 reports results based on risdiplam list price), while Figure 43 shows the cost-effectiveness plane. The probabilistic analysis in the Roche model relied on extended dominance between all the DMTs and BSC, therefore the probability of cost-effectiveness between risdiplam and BSC only could not be extracted.

Table 118: Cost effectiveness results for risdiplam versus BSC in the EAG base-case (list prices)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)	Severity modifier
Deterministic								
Risdiplam	[REDACTED]	25.96	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
BSC	[REDACTED]	12.91	[REDACTED]	[REDACTED]	13.05	[REDACTED]	£227,628	£133,899
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year								

Table 119: Cost effectiveness results for risdiplam versus BSC in the EAG base-case (using risdiplam PAS price)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)	Severity modifier
Deterministic								
Risdiplam		25.96						
BSC		12.91			13.05			
Probabilistic								
Risdiplam								
BSC								
Probability cost-effective							NA	
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year								

Figure 43: Cost-effectiveness plane for the EAG base-case analysis (presymptomatic)

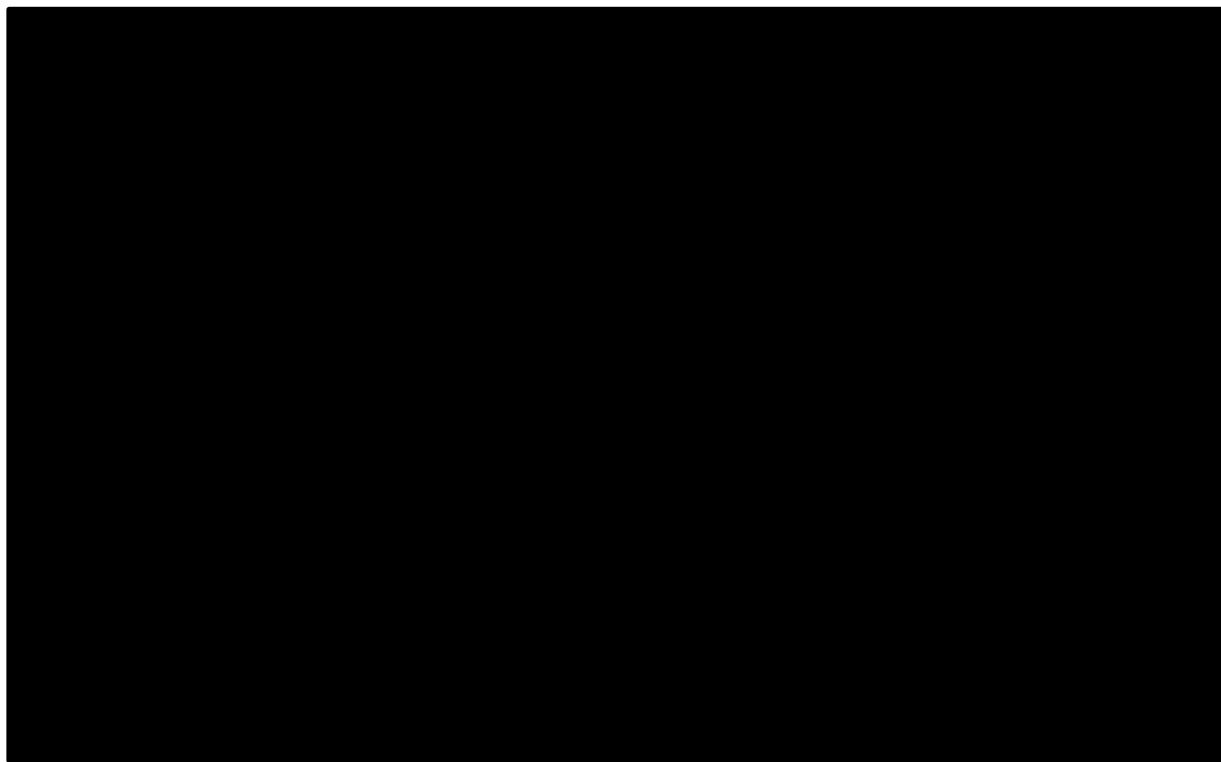
Abbreviations: BSC = best supportive care; QALY = quality-adjusted life year; WTP = willingness to pay

15.2.1.2 One-way sensitivity analysis

Parameters with the biggest impact on the ICER compared to BSC were the drug price of risdiplam, disease related costs for children at the “not sitting” and “sitting” health-states, the risk of permanent ventilation and disease related costs for adults at “not sitting” and “walking” health states. (Figure 44)

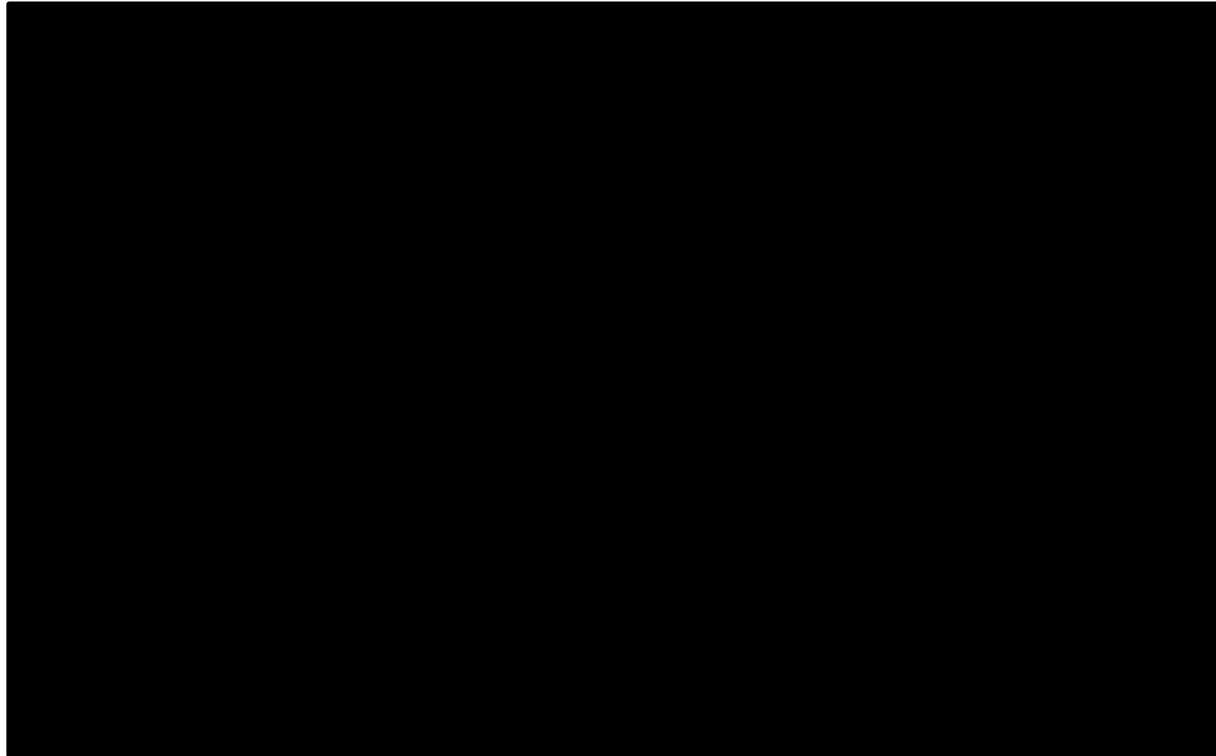
Parameters with the biggest impacts on costs were the drug price of risdiplam, disease-related costs at “not sitting” and “sitting”, and the risk of permanent ventilation. (Figure 45) Parameters with the biggest impact on quality of life were patient utilities at “walking” and “standing”, the treatment benefit of receiving risdiplam, and the risks of long-term motor decline for risdiplam. (Figure 46)

Figure 44: One-way sensitivity analysis on the ICER between risdiplam and BSC for the EAG base-case (presymptomatic)



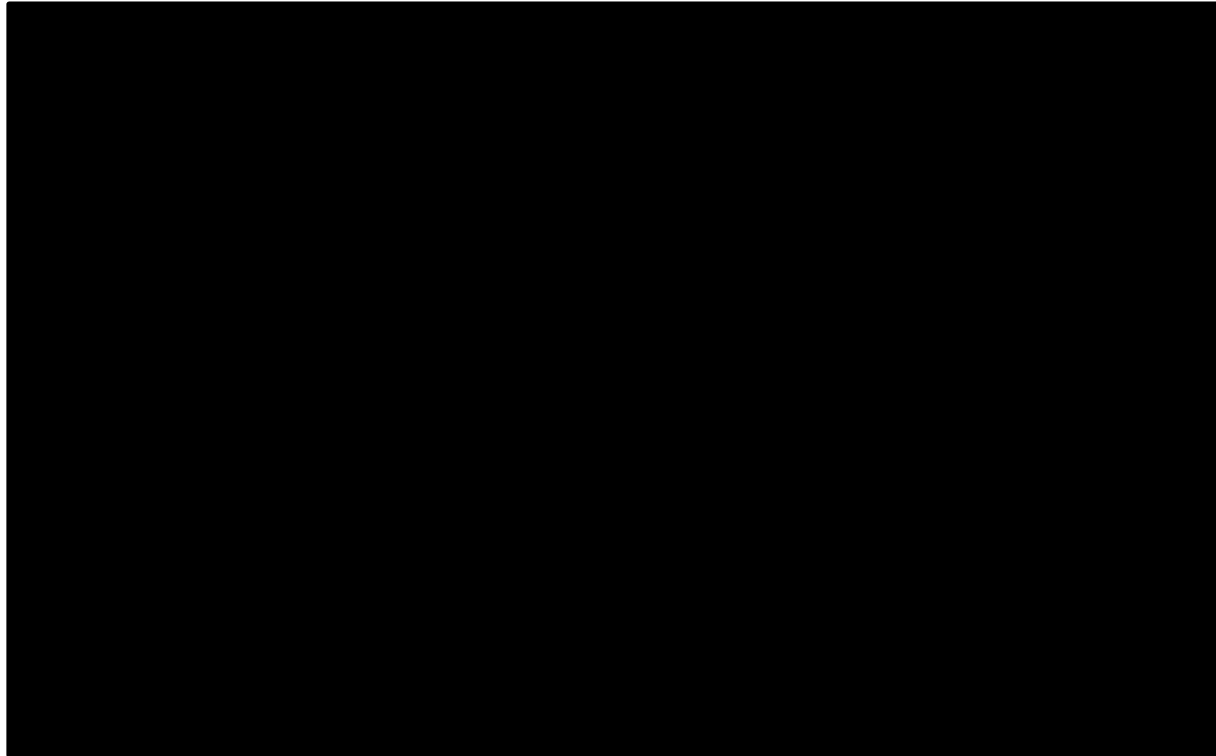
Abbreviations: BSC = best supportive care; HSUV = health state utility value; ICER = incremental cost-effectiveness ratio; PV = permanent ventilation; QALY = quality-adjusted life year

Figure 45: One-way sensitivity analysis on incremental costs between risdiplam and BSC for the EAG base-case (presymptomatic)



Abbreviations: BSC = best supportive care; PV = permanent ventilation

Figure 46: One-way sensitivity analysis on incremental QALYs between risdiplam and BSC for the EAG base-case (presymptomatic)



Abbreviations: BSC = best supportive care; HSUV = health state utility value; PV = permanent ventilation; QALY = quality-adjusted life year

15.2.1.3 Scenario analyses

Base-case scenarios: risdiplam vs BSC

The scenario analysis between risdiplam and BSC showed that scenarios with the biggest impact on the ICER were the choice of time horizon being less than lifetime, the patient health-state related costs, and pooling the impact on carers and patients together. (Table 120)

Table 120: Scenario analysis for risdiplam versus BSC in the EAG base-case (using risdiplam PAS price) (presymptomatic)

Technologies	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)	% change
Base-case					
Risdiplam	██████	13.05	████	██████	-
Scenarios					
Patient and carer utilities ^a	██████	13.05	████	██████	-43%
Utilities from Roche base-case ^b	██████	13.05	████	██████	-1%
Costs from Roche base-case	██████	13.05	████	██████	137%
Time horizon of 10 years	██████	1.00	████	Risdiplam dominant	-
Time horizon of 30 years	██████	6.07	████	Risdiplam dominant	-
Assuming price of risdiplam = £0	██████	13.05	████	Risdiplam dominant	-
^a Carer utilities were based on absolute decrements from Lo et al. (2022) assuming 1 carer and following average carer characteristics in the study. ^b Negative utilities assumed equal to 0 Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year					

Risdiplam compared to nusinersen (equivalent effectiveness)

The scenario analysis for the presymptomatic population comparing risdiplam with nusinersen, focusing on patient HRQoL, including the PAS discount for risdiplam, showed that nusinersen was equally effective and ██████████, ██████████. Table 121 reports the results of all scenarios comparing risdiplam with nusinersen and OA; please note that these were based on list prices for nusinersen or OA.

Risdiplam compared to nusinersen (naïve comparison)

The scenario for the presymptomatic population comparing risdiplam with nusinersen, focusing on patient HRQoL, including the PAS discount for risdiplam, showed that risdiplam was ██████████

Risdiplam compared to OA (equivalent effectiveness)

The scenario analysis for the presymptomatic population comparing risdiplam with OA, focusing on patient HRQoL, including the PAS discount for risdiplam, showed that OA was

Table 121: Scenario analysis for risdiplam versus nusinersen and OA using the EAG approach (presymptomatic)

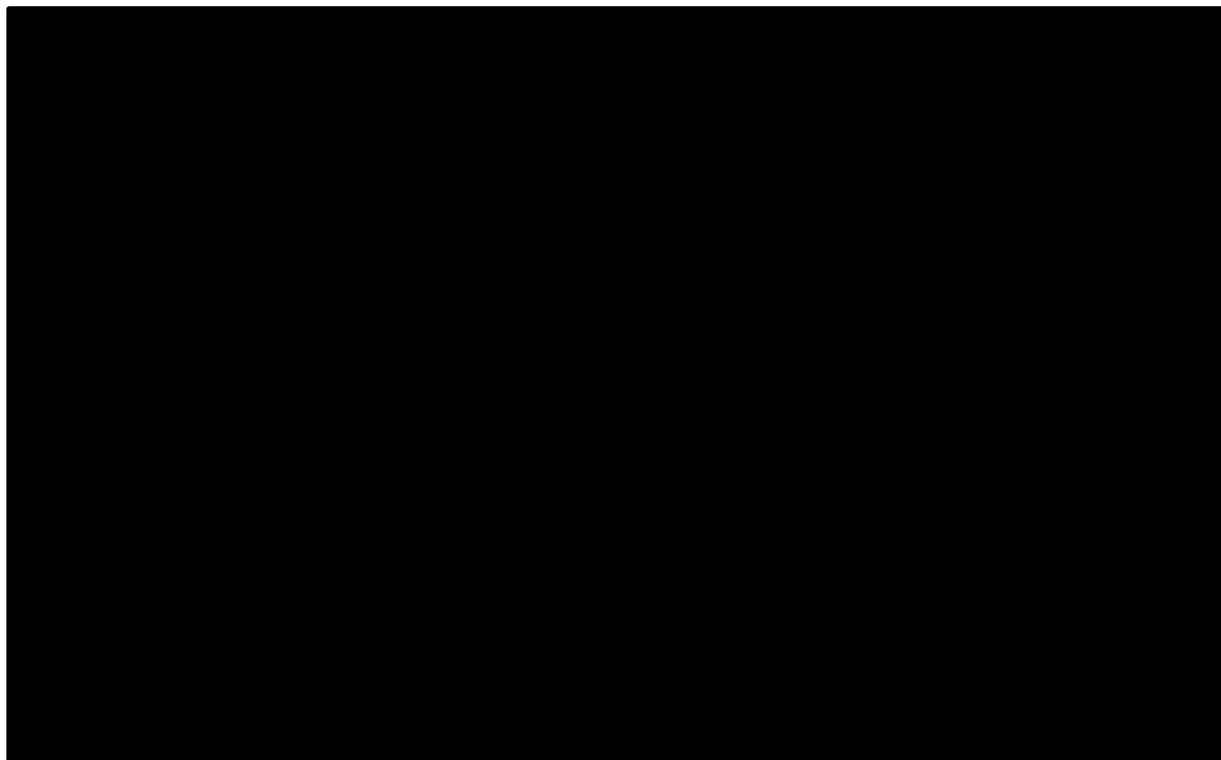
Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)	Severity modifier
Deterministic: risdiplam vs nusinersen (equivalent effectiveness)								
Risdiplam	£1,000,000	25.96	1.0	£0				
Nusinersen	£1,000,000	25.96	1.0	£0	0	0	£0	-
Deterministic: risdiplam vs nusinersen (naïve comparison)								
Risdiplam	£1,000,000	25.96	1.0	£0				
Nusinersen	£1,000,000	25.95	1.0	£0	0	0	£0	-
Deterministic: risdiplam vs OA (equivalent effectiveness)								
Risdiplam	£1,000,000	25.96	1.0	£0				
OA	£1,000,000	25.96	1.0	£0	0	0	£0	-
Probabilistic: risdiplam vs nusinersen (naïve comparison)								
Risdiplam	£1,000,000		1.0	£0				
Nusinersen	£1,000,000		1.0	£0		0	£0	-
Probability cost effective							NA	
Probabilistic: risdiplam vs OA (equivalent effectiveness)								
Risdiplam	£1,000,000		1.0	£0				
OA	£1,000,000		1.0	£0		0	£0	-
Probability cost effective							NA	
Abbreviations: BSC = best supportive care ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year								

15.2.1.4 One-way sensitivity analyses for the scenario with disease modifying therapies

Risdiplam versus nusinersen (naïve comparison)

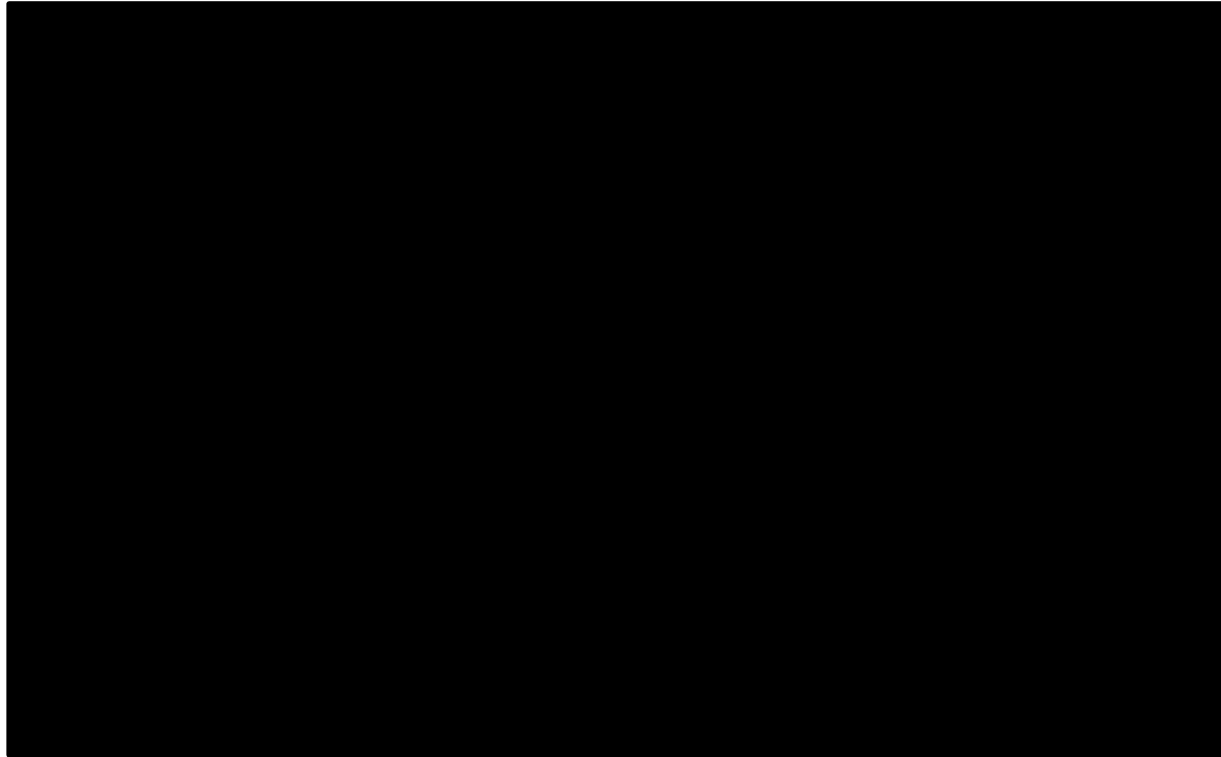
Parameters with the biggest impacts on costs were the drug price of nusinersen, the drug price of risdiplam, the relative effectiveness for moving from “sitting” to “standing”. (Figure 47) Parameters with the biggest impacts on utilities were the relative effectiveness of moving from “sitting” to “standing” and the effectiveness of moving from “not sitting” to “sitting”. (Figure 48)

Figure 47: One-way sensitivity analysis on incremental costs between risdiplam and nusinersen for the EAG approach (presymptomatic)



Abbreviations: OR = odds ratio

Figure 48: One-way sensitivity analysis on incremental QALYs between risdiplam and nusinersen for the EAG approach (presymptomatic)

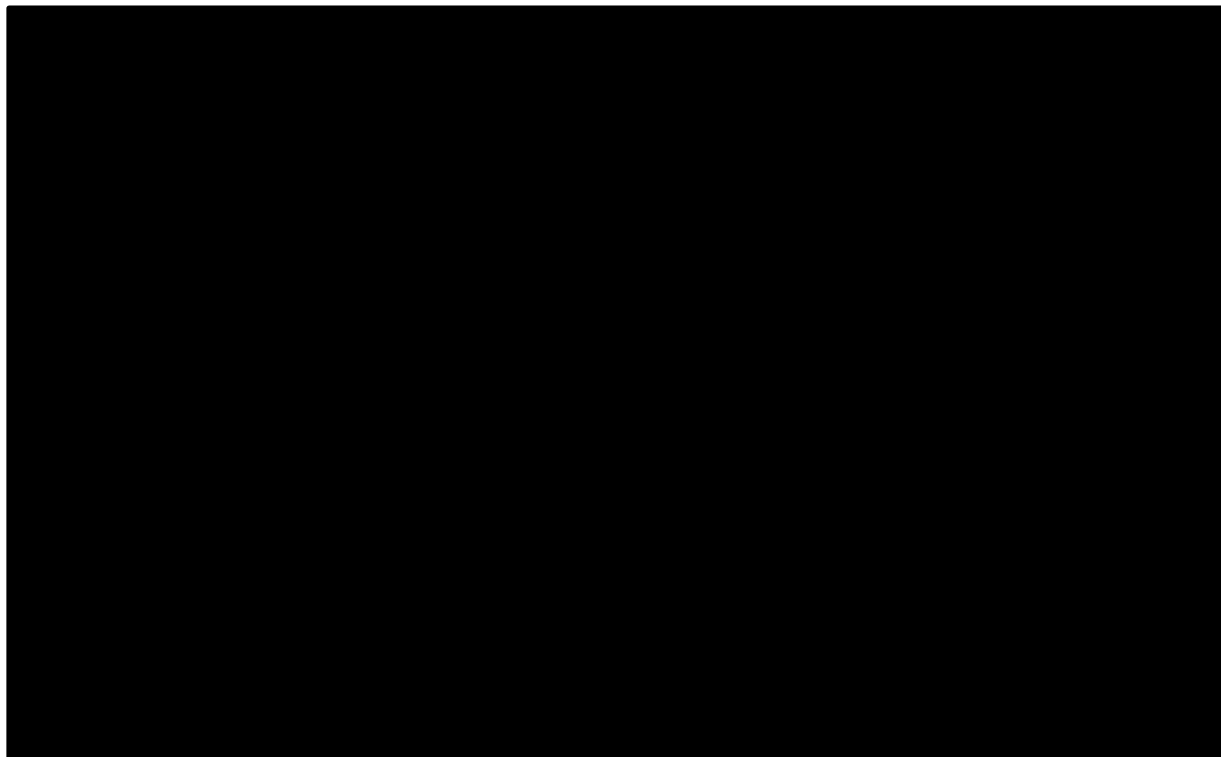


Abbreviations: HSUV = health state utility value; OR = odds ratio; QALY = quality-adjusted life year

Risdiplam versus OA (equivalent effectiveness)

Parameters with the largest impacts on costs were the drug prices of risdiplam and OA, respectively (see Figure 49). Parameters with the largest impacts on utilities were relative effectiveness for moving from “not sitting” to “sitting” and “sitting” to “standing” (see Figure 50).

Figure 49: One-way sensitivity analysis on incremental costs between risdiplam and OA (presymptomatic)



Abbreviations: OA = onasemnogene abeparvovec; OR = odds ratio; p.a. = per annum; RDI = relative dose intensity

Figure 50: One-way sensitivity analysis on incremental QALYs between risdiplam and OA (presymptomatic)



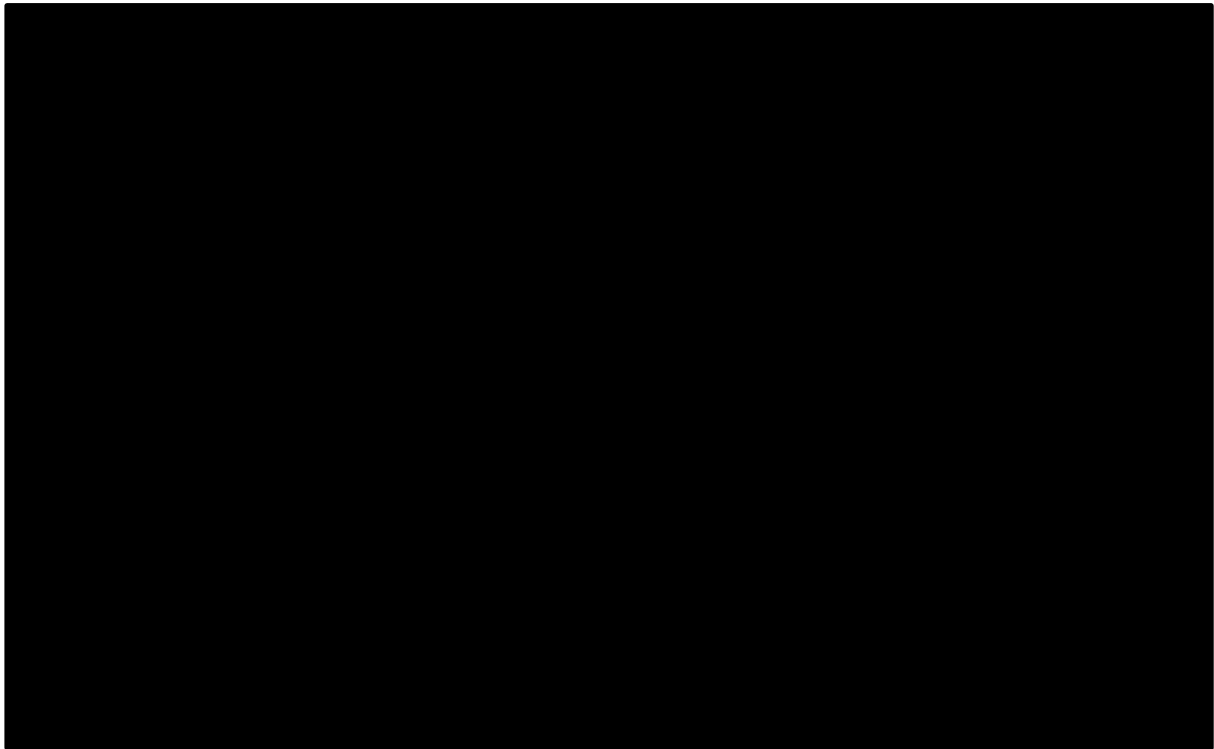
Abbreviations: kg = kilogram; OA = onasemnogene abeparvovec; OR = odds ratio; p.a = per annum; QALY = quality-adjusted life year

15.2.2.1 Deterministic base-case analysis

Probabilistic results showed that risdiplam was more costly [REDACTED] [REDACTED]) and more effective [REDACTED] [REDACTED]) with an ICER of [REDACTED] QALY. Applying a severity modifier of 1.7 led to an ICER of [REDACTED] QALY. Table 123 reports deterministic and probabilistic results (Table 122 reports the results based on risdiplam list price), and Figure 51 shows the cost-effectiveness plane.

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)	Severity modifier
Deterministic								
Risdiplam	[REDACTED]	19.05	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
BSC	[REDACTED]	3.98	[REDACTED]	[REDACTED]	15.06	[REDACTED]	£370,959	£218,211
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year								

[illegible]

Figure 51: Cost-effectiveness plane for the EAG base-case analysis (type 1)

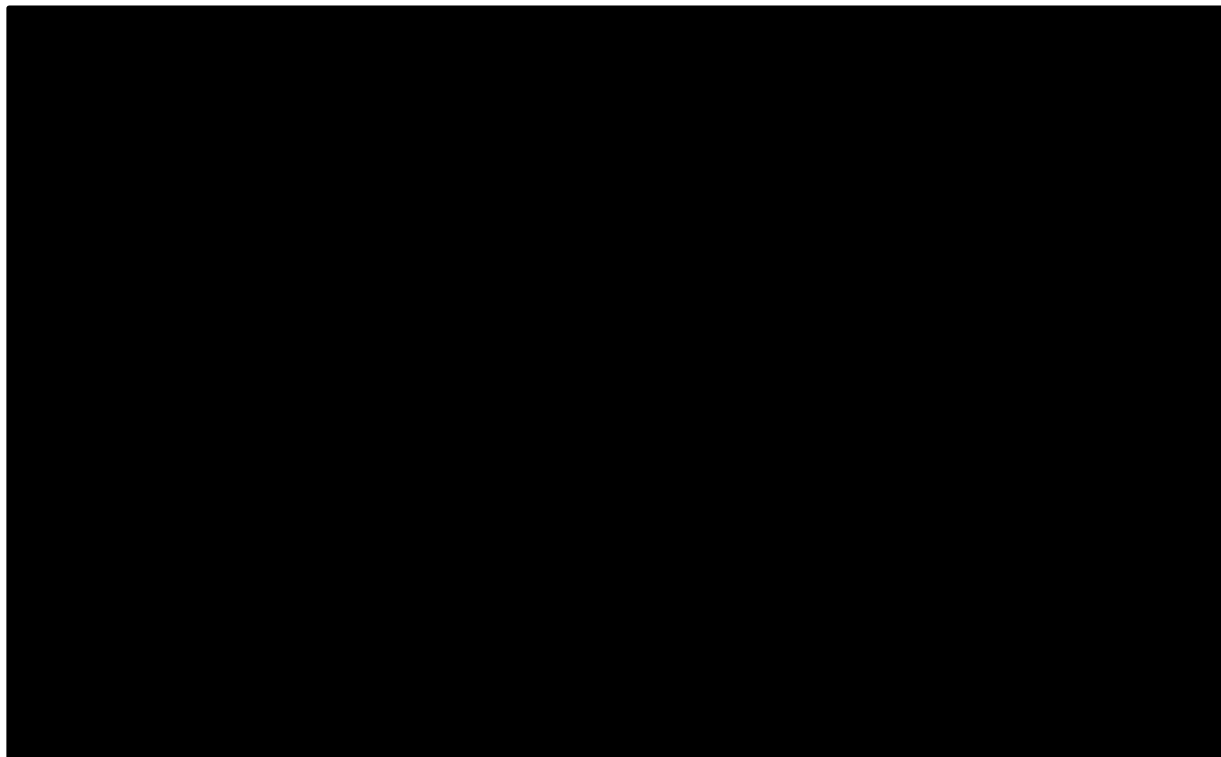
Abbreviations: QALY = quality-adjusted life-year; WTP = willingness to pay

15.2.2.2 One-way sensitivity analysis

Parameters with the biggest impact on the ICER compared to BSC were the overall survival benefit of risdiplam, the drug cost of risdiplam, disease-related costs at “sitting”, and the differences in permanent ventilation risks. (Figure 52)

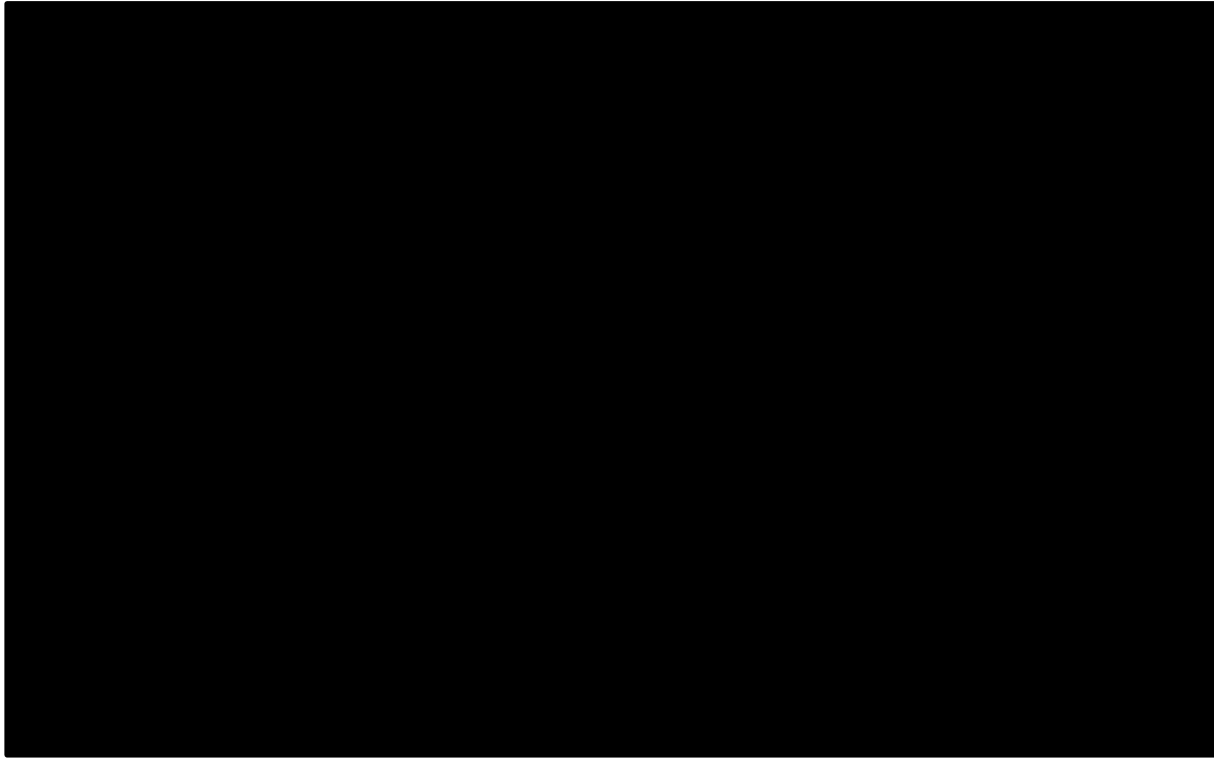
Parameters with the biggest impacts on costs were difference in overall survival risk, the drug cost of risdiplam, disease-related costs for children and adults at “sitting”, and the risk and cost of permanent ventilation. (Figure 53) Parameters with the largest impact on patient quality of life were utilities at “sitting”, the treatment benefit of risdiplam, treatment utilities at “standing” and “walking”, and the risk of permanent ventilation. (Figure 54)

Figure 52: One-way sensitivity analysis on the ICER between risdiplam and BSC for the EAG base-case (type 1)



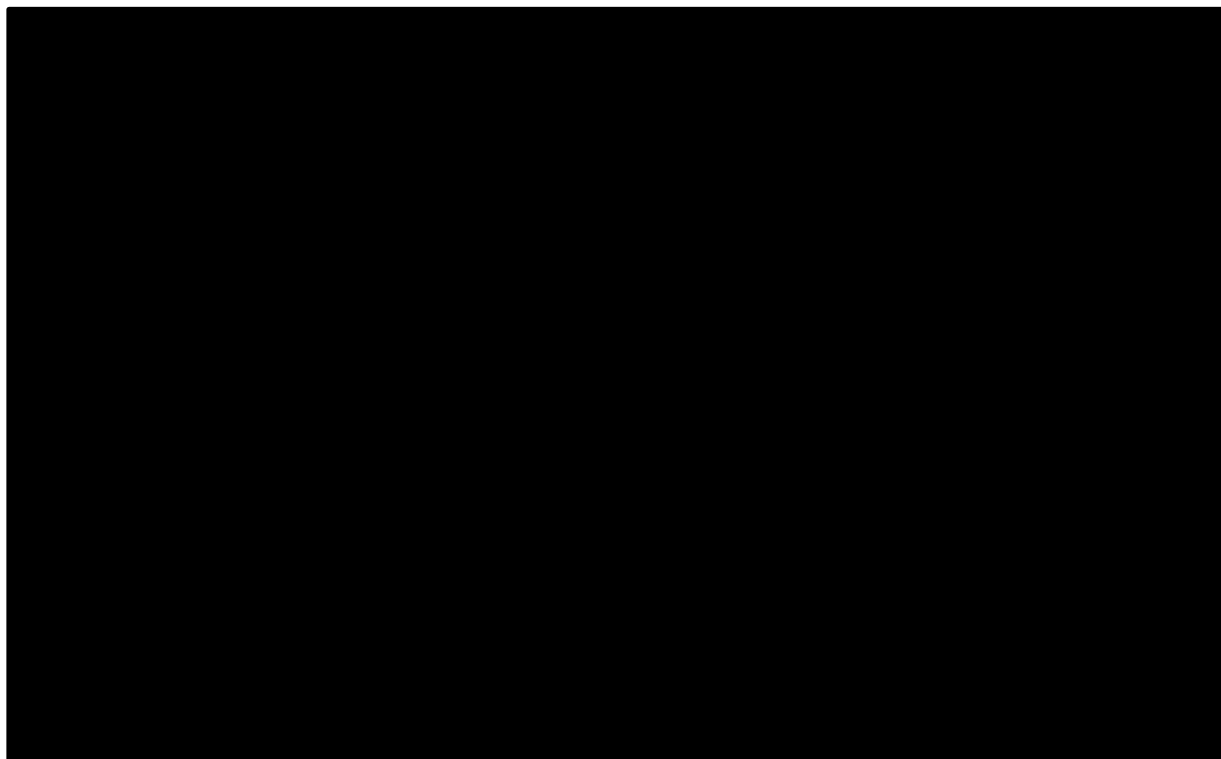
Abbreviations: HR = hazard ratio; HSUV = health state utility value; ICER = incremental cost-effectiveness ratio; OS = overall survival; QALY = quality-adjusted life year

Figure 53: One-way sensitivity analysis on incremental costs between risdiplam and BSC for the EAG base-case (type 1)



Abbreviations: EFS = event-free survival; HR = hazard ratio; OS = overall survival

Figure 54: One-way sensitivity analysis on incremental QALYs between risdiplam and BSC for the EAG base-case (type 1)



Abbreviations: BSC = best supportive care; EFS = event-free survival; HR = hazard ratio; HSUV = health state utility value; OS = overall survival; QALY = quality-adjusted life year

15.2.2.3 Scenario analyses

Base-case scenarios: risdiplam vs BSC

The scenario analysis between risdiplam and BSC showed that scenarios with the biggest impact on the ICER were using the utilities from the base-case analysis in the Roche submission, changing the length of the time horizon, and pooling patient and carer utilities. Table 124 shows the results.

Table 124: Scenario analysis for risdiplam versus BSC in the EAG base-case (type 1)

Technologies	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)	% change
Base-case					
Risdiplam	████████	15.06	████	████	-
Scenarios					
Company relative effectiveness estimates	████████	15.06	████	████	-0.3%
Patient and carer utilities	████████	15.06	████	████	-47.17%
Utilities from Roche base-case*	████████	15.06	████	████	82.0%
Costs from Roche base-case	████████	15.06	████	████	-13.2%
Time horizon of 10 years	████████	4.14	████	████	-61.3%
Time horizon of 30 years	████████	11.13	████	████	-11.7%
Assuming risdiplam cost = £0	████████	15.06	████	████	-
*Negative utilities assumed equal to 0 Abbreviations: ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year					

Risdiplam compared to nusinersen

The base-case analysis for the type 1 population comparing risdiplam with nusinersen, focusing on patient HRQoL, including the PAS discount for risdiplam, showed that risdiplam ██████████ than ██████████ nusinersen, ██████████. Table 125 shows the results comparing risdiplam with nusinersen and with OA. Please note that PAS discounts were not included for nusinersen or OA, only list prices were used.

Risdiplam compared to OA

The base-case analysis for the type 1 population comparing risdiplam with OA, focusing on patient HRQoL, including the PAS discount for risdiplam, showed that risdiplam ██████████ OA, ██████████.

Table 125: Scenario analysis for risdiplam versus nusinersen and OA using the EAG approach (type 1)

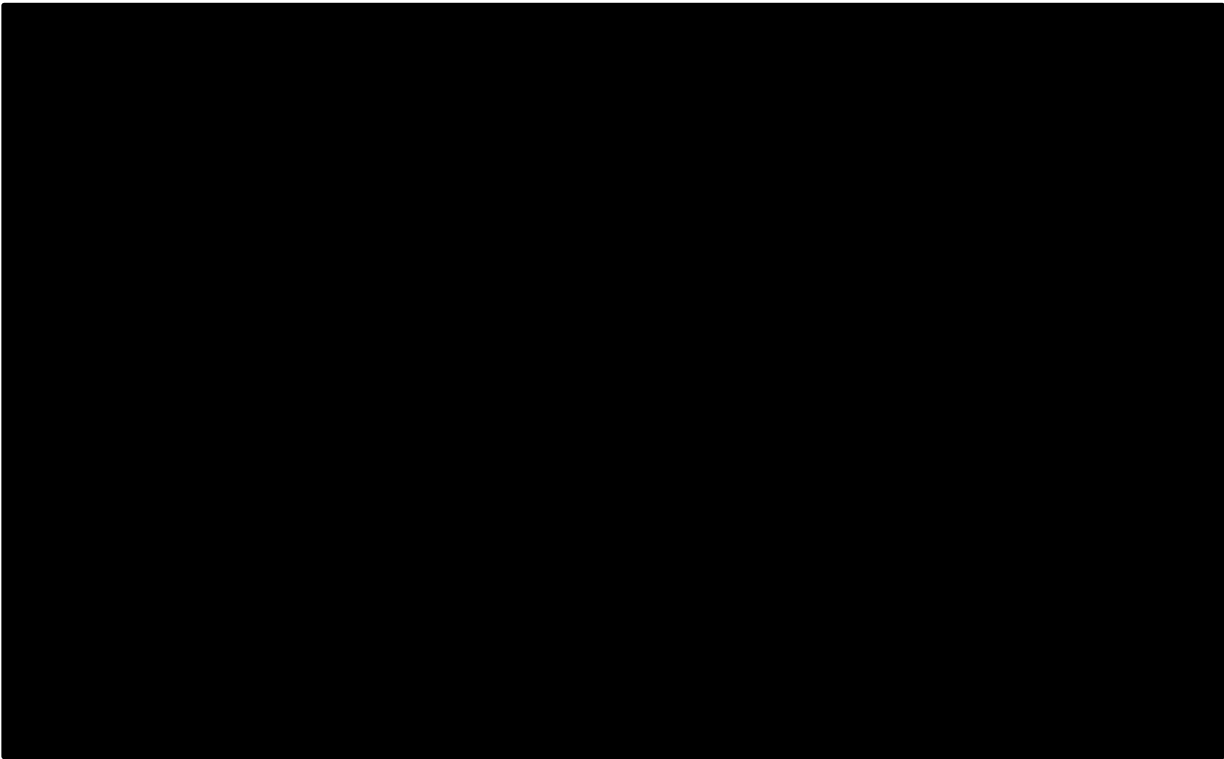
Appendix (type 1)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Deterministic: Risdiplam vs nusinersen							
Risdiplam	██████	19.05	████				
Nusinersen	██████	11.66	████	██████	7.38	████	██████████
Deterministic: Risdiplam vs OA							
Risdiplam	██████	19.05	████				
OA	██████	18.82	████	██████	0.23	████	██████████
Probabilistic: Risdiplam vs nusinersen							
Risdiplam	██████		████				
Nusinersen	██████		████	██████		████	██████████
Probability cost effective						NA	
Probabilistic: Risdiplam vs OA							
Risdiplam	██████		████				
OA	██████		████	██████		████	██████████
Probability cost effective						NA	
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year							

15.2.2.4 One-way sensitivity analyses for the scenario with disease modifying therapies Risdiplam versus nusinersen

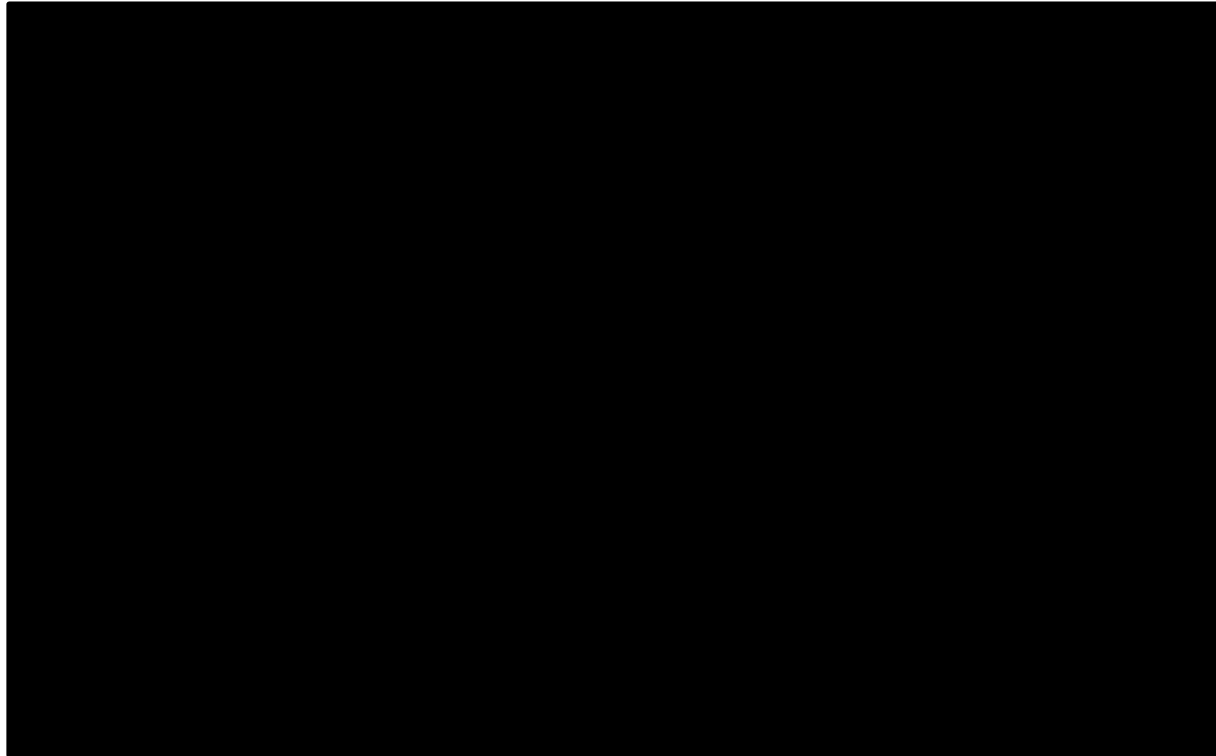
Parameters with the biggest impacts on costs were the overall survival hazard ratio between risdiplam and nusinersen, the cost of nusinersen, the hazard ratio in permanent ventilation, and the odds ratio of “sitting” to “standing”.(Figure 55) Parameters with the biggest impacts on quality of life were the hazard ratio in overall survival, the odds ratio from “sitting” to “standing”, and the hazard ratio in the risk of permanent ventilation.(Figure 56)

Figure 55: One-way sensitivity analysis on incremental costs between risdiplam and nusinersen (type 1)



Abbreviations: EFS = event-free survival; HR = hazard ratio; OR = odds ratio; OS = overall survival

Figure 56: One-way sensitivity analysis on incremental QALYs between risdiplam and nusinersen (type 1)

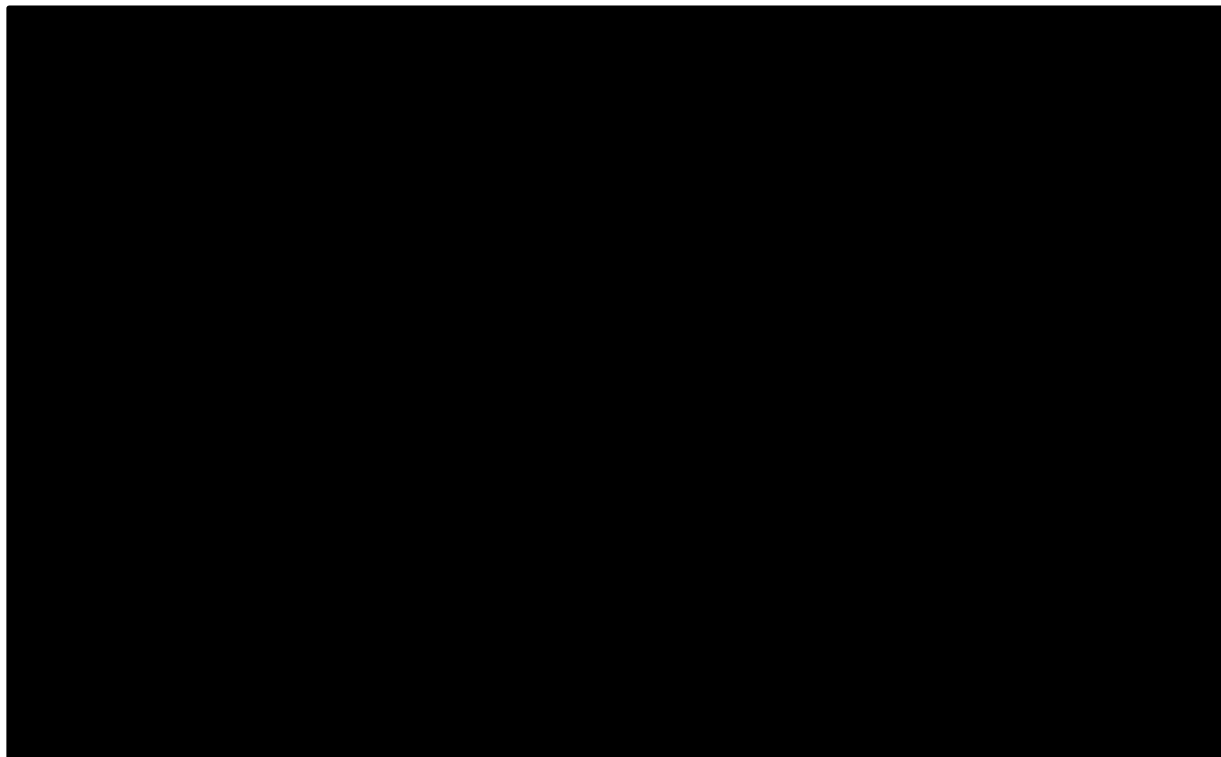


Abbreviations: DMT = disease-modifying therapy; EFS = event-free survival; HR = hazard ratio; HSUV = health state utility value; OR = odds ratio; OS = overall survival

Risdiplam versus OA

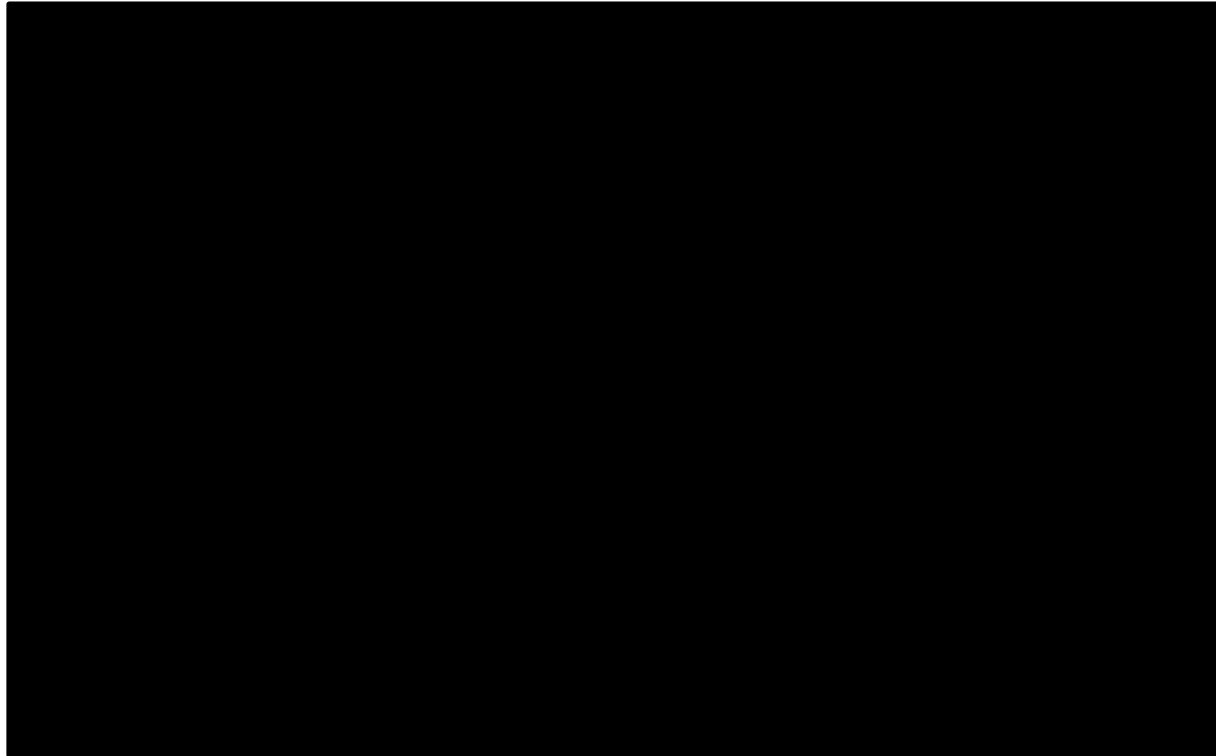
Parameters with the biggest impacts on costs between risdiplam and OA were the drug cost of OA, the drug cost of risdiplam, the odds ratio of “not sitting” to “sitting”, the odds ratios in overall survival, and disease-related costs at sitting (see Figure 57). Parameters with the biggest impacts on quality of life were the risk of permanent ventilation, the odds ratio from “not sitting” to “sitting”, and the hazard ratio in overall survival (see Figure 58).

Figure 57: One-way sensitivity analysis on incremental costs between risdiplam and OA (type 1)



Abbreviations: BSC = best supportive care; HR = hazard ratio; OA = onasemnogene abeparvovec; OR = odds ratio

Figure 58: One-way sensitivity analysis on incremental QALYs between risdiplam and OA (type 1)



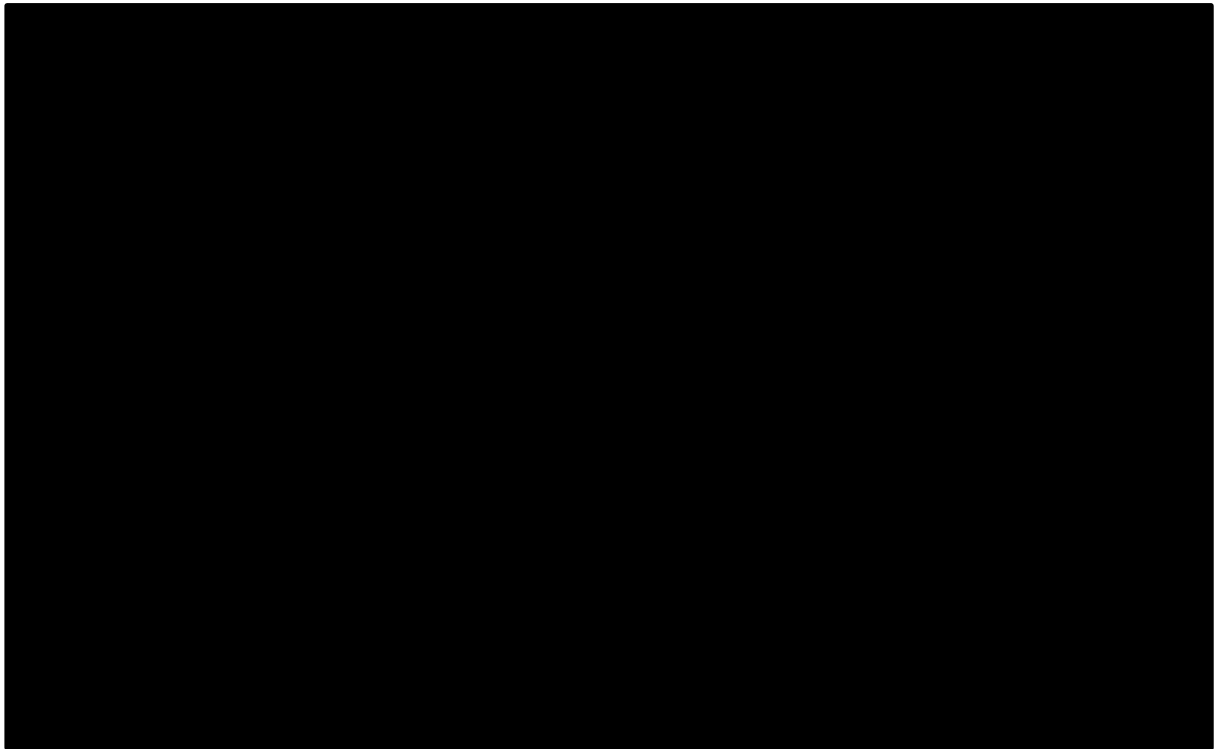
Abbreviations: DMT = disease-modifying therapy; EFS = event-free survival; HR = hazard ratio; HSUV = health state utility value; OR = odds ratio; OS = overall survival; QALY = quality-adjusted life year

15.2.3.1 Deterministic base-case analysis

Probabilistic results showed that risdiplam was and () with an ICER of /QALY. Applying a severity modifier of 1.2 led to an ICER of QALY. Table 127 reports deterministic and probabilistic results (Table 126 reports the results based on risdiplam list price), Figure 59 shows the cost-effectiveness plane.

[illegible]

Technology	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)	Severity modifier
Deterministic								
Risdiplam	[REDACTED]	24.47	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
BSC	[REDACTED]	22.03	[REDACTED]	[REDACTED]	2.44	[REDACTED]	[REDACTED]	[REDACTED]
Probabilistic								
Risdiplam	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
BSC	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Probability cost-effective							NA	
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year								

Figure 59: Cost-effectiveness plane for the EAG base-case analysis (type 2/3)

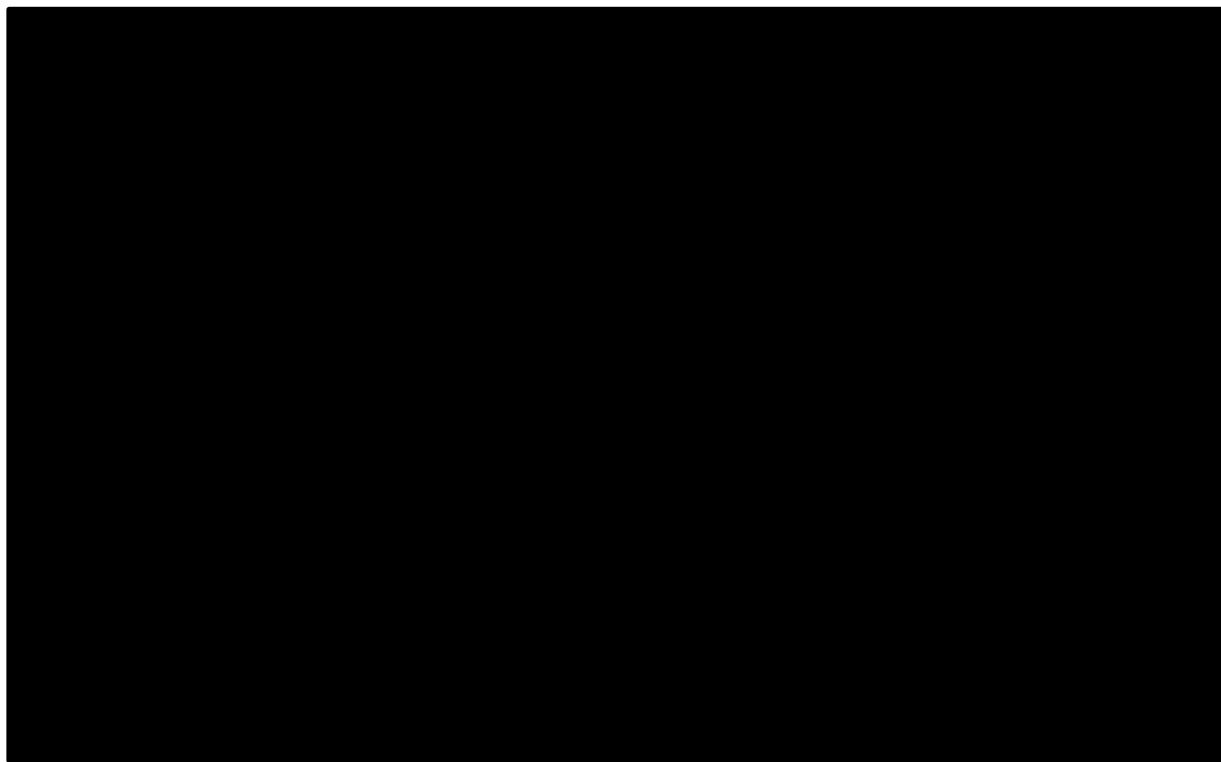
Abbreviations: BSC = best supportive care; QALY = quality-adjusted life year

15.2.3.2 One-way sensitivity analysis

Parameters with the biggest impact on the ICER were the drug cost of risdiplam, disease-related costs at “not sitting” for adults, utilities for “sitting without support”, and disease-related costs at “sitting without support” for adults. (Figure 60)

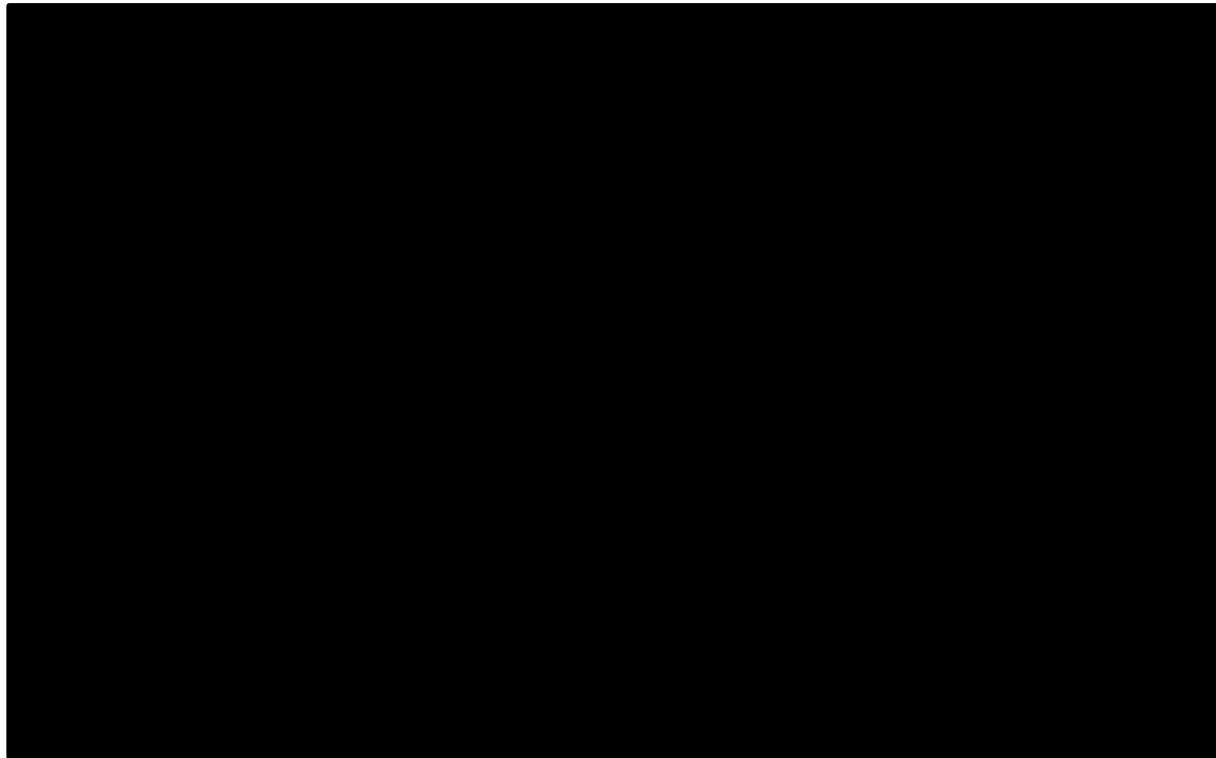
Parameters with the biggest impact on costs were the drug cost of risdiplam, disease-related costs at “not sitting” and “sitting without support” for adults, and disease-related costs at “not sitting” for children. (Figure 61) Parameters with the biggest impact on quality of life were utilities for “sitting without support” and “not sitting”, the treatment benefit of risdiplam, and utility at “sitting with support”. (Figure 62)

Figure 60: One-way sensitivity analysis on the ICER between risdiplam and BSC for the EAG base-case (type 2/3)



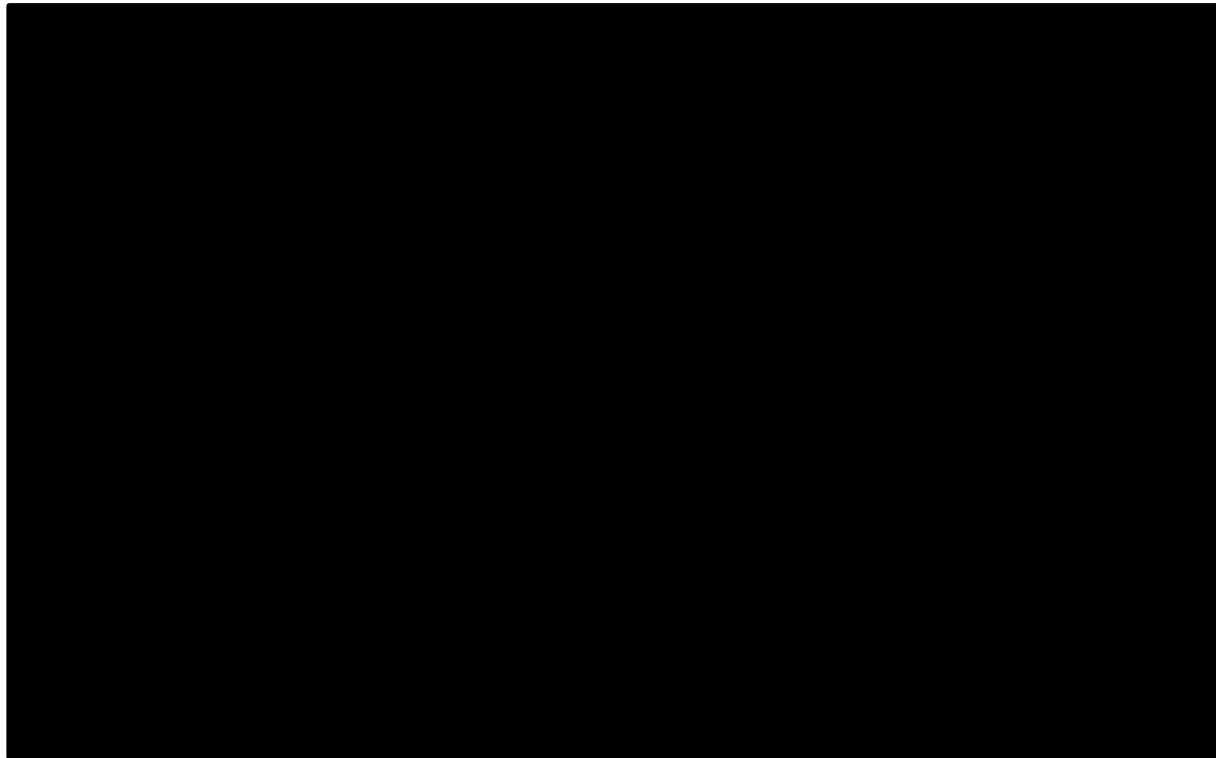
Abbreviations: BSC = best supportive care; HSUV = health state utility value; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Figure 61: One-way sensitivity analysis on incremental costs between risdiplam and BSC for the EAG base-case (type 2/3)



Abbreviations: BSC = best supportive care; DMT = disease-modifying therapy

Figure 62: One-way sensitivity analysis on incremental QALYs between risdiplam and BSC for the EAG base-case (type 2/3)



Abbreviations: BSC = best supportive care; DMT = disease-modifying therapy; HSUV = health state utility value; QALY = quality-adjusted life year

15.2.3.3 Scenario analyses

Base-case scenarios: risdiplam vs BSC

The scenario analysis between risdiplam and BSC showed that scenarios with the biggest impact on the ICER were using utilities from the SUNFISH trial, using utilities from the base-case in the Roche submission, shortening the time horizon to 10 years. Table 128 shows the results.

Table 128: Scenario analysis for risdiplam versus BSC in the EAG base-case (type 2/3)

Technologies	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)	% change
Base-case					
Risdiplam	██████	2.44	██	██████	-
Scenarios					
ITT SUNFISH incl. Asia	██████	2.41	██	██████	██
Patient and carer utilities	██████	2.44	██	██████	██████
Utilities from Roche base-case*	██████	2.44	██	██████	██████
Utilities from the SUNFISH trial ⁴⁴	██████	2.44	██	██████	██████
Including the impact of bulbar dysfunction from Roche base-case	██████	2.44	██	██████	██
Including the impact of bulbar dysfunction from the van der Heul et al. 2019 ⁷³	██████	2.44	██	██████	██
Costs from Roche base-case	██████	2.44	██	██████	██████
Time horizon of 10 years	██████	2.44	██	██████	██████
Time horizon of 30 years	██████	2.44	██	██████	██
Assuming risdiplam cost = £0	██████	2.44	██	██████████████	█
*Negative utilities assumed equal to 0 Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; ITT = intention to treat; LY = life year; QALY = quality-adjusted life year					

Risdiplam compared to nusinersen

The base-case analysis for the type 2 and 3 population comparing risdiplam with nusinersen, focusing on patient HRQoL, including the PAS discount for risdiplam, showed that risdiplam ██████████ than ██████████ nusinersen, ██████████. Table 129 presents the results. Please note, these do not include PAS discounts for nusinersen, only the list price was used.

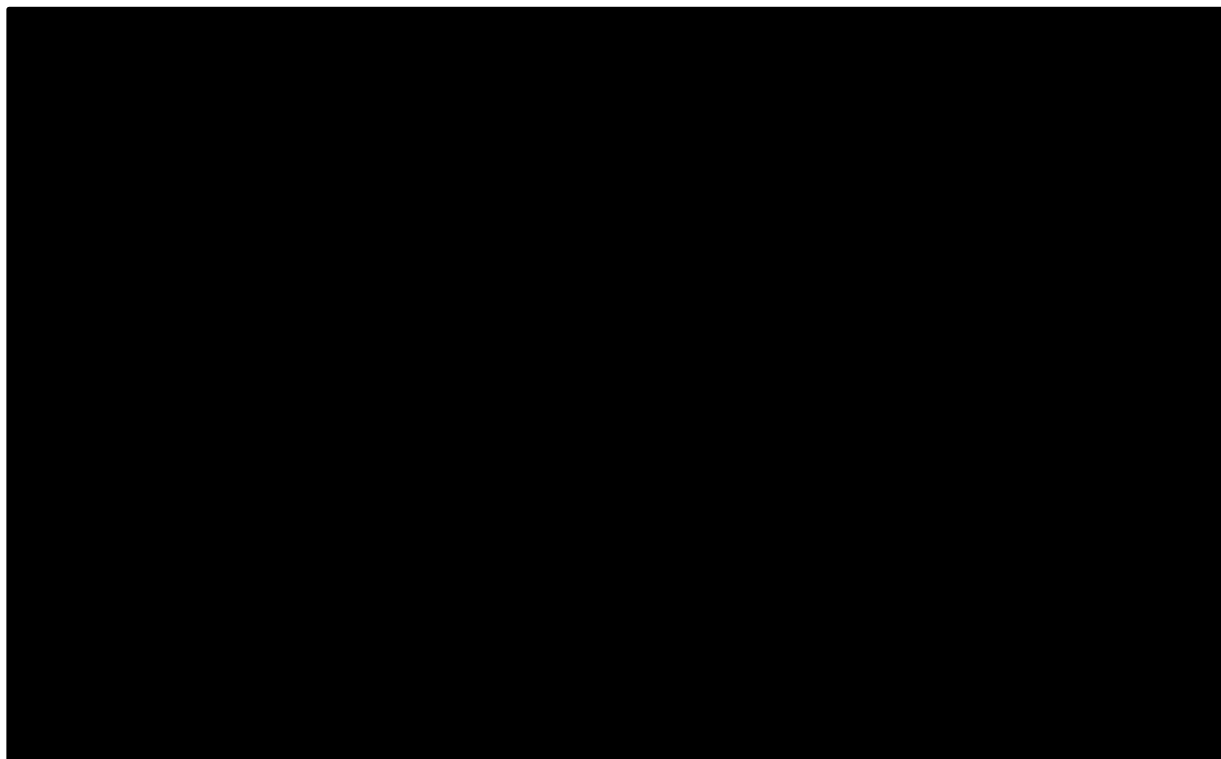
Table 129: Scenario analysis for risdiplam versus nusinersen using the EAG approach (type 2/3)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Deterministic							
Risdiplam	████████	24.47	████	-	-	-	-
Nusinersen	████████	23.52	████	████████	0.95	████	██████████
Probabilistic							
Risdiplam	████████		████				
Nusinersen	████████		████	████████		████	██████████
Probability cost-effective						N/A	
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year							

15.2.3.4 One-way sensitivity analyses for the scenario with disease modifying therapies Risdiplam versus nusinersen

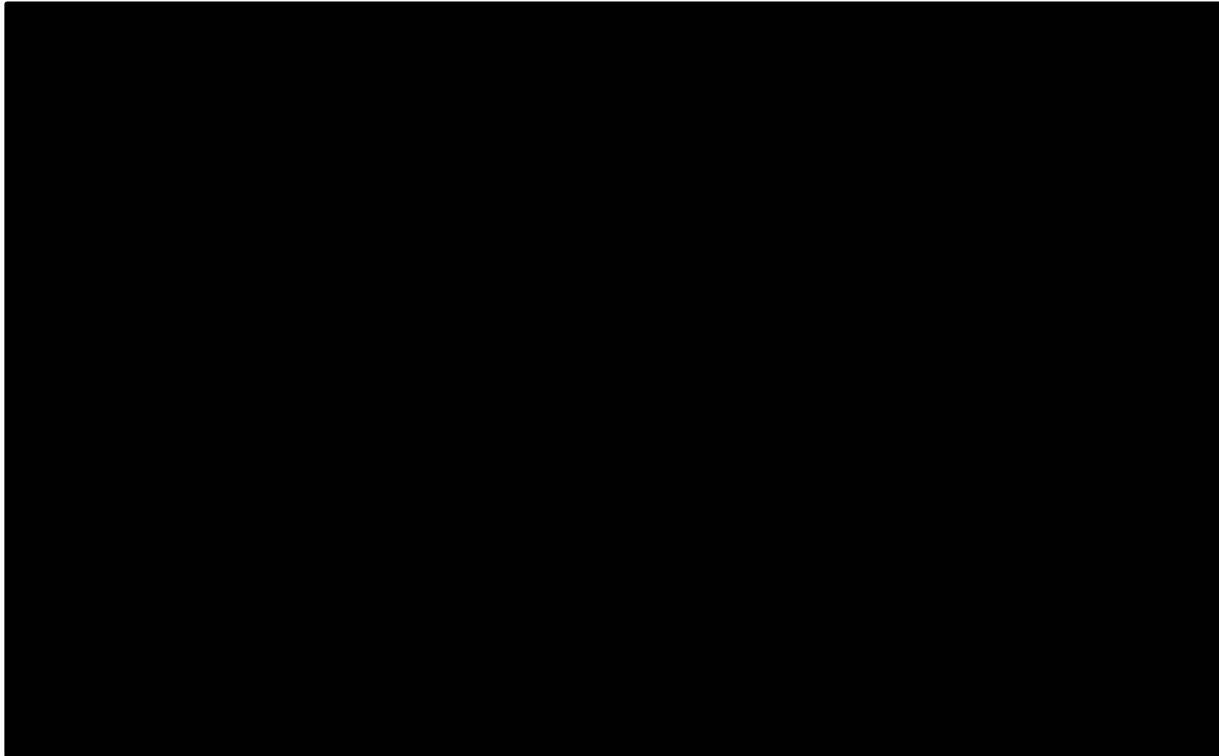
Parameters with the biggest impact on costs were the drug cost of nusinersen, the drug cost of risdiplam, disease-related costs for adults at “not sitting” and “sitting without support”. (Figure 63) Parameters with the biggest impact on patient quality-of-life were the odds ratio for responding to treatment, the utility at “sitting without support”, the treatment benefit of risdiplam and nusinersen respectively, and utility at “not sitting”. (Figure 64)

Figure 63: One-way sensitivity analysis on incremental costs between risdiplam and nusinersen (type 2/3)



Abbreviations: DMT = disease-modifying therapy; RULM = Revised Upper Limb Module

Figure 64: One-way sensitivity analysis on incremental QALYs between risdiplam and nusinersen (type 2/3)



Abbreviations: DMT = disease-modifying therapy; HSUV = health state utility value; QALY = quality-adjusted life year; RULM = Revised Upper Limb Module

15.3 Qualitative analyses surrounding economic impact and finances

This section considers the results of the qualitative framework analysis described in Section 9 specifically in relation to the economic impacts of SMA and treatment. Qualitative results surrounding clinical effectiveness outcomes is presented in Section 13.5.

The financial burden on patients and families of managing SMA and the overall cost to the health service were frequently mentioned within the submissions and case studies. Some of the submissions from patient experts and organisations highlighted the need to use a wide range of health services to both monitor and manage SMA. This included: physiotherapy; hydrotherapy; hippotherapy; hospitalisations because of falls; dieticians; speech and language therapy; BiPAP ventilation where required; gastrostomy if needed; surgery (e.g. for scoliosis); and occupational therapy. Potential inequalities in the availability of NHS services amongst different populations and across the UK was highlighted within submissions. A submission from a professional organisation highlighted differences in availability of health services between adults with SMA and children with SMA, as well as by a professional expert submission.

“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 submission

“Orthotics provision is fragmented nationally as well as management of orthopaedic problems.” – Professional expert submission

A similar disparity across the UK in the ability to access Continuing Care funding was also highlighted by one patient expert submission. Not being able to access to some services through the NHS could also lead to families paying for private treatment.

“Unfortunately, physio comes in blocks on the NHS so it is not continuous throughout the year. These voids are filled with paid, private physio.” – Patient expert submission 2 (carer for a child with SMA)

[REDACTED]

As well as the potential of paying for services beyond the NHS, submissions and case studies also often mentioned the need for families and carers to buy their own specialist equipment to help facilitate activities of daily living and maintain a level of independence. Equipment and devices mentioned included: equipment needed for physiotherapy; wheelchairs with modifications not covered by standard healthcare services; accessible vehicles; and hot tubs for hydrotherapy. The cost of accessing these services and equipment was noted to be substantial and individuals, carers and wider families noted that they had to fundraise to be able to afford these pieces of equipment, highlighting the wider impact of SMA on carers and families.

“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” – Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; carer of child with SMA

“[...] 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.” – Patient expert submission 2 (carer for child with SMA)

Despite the significant costs to individuals and families associated with managing SMA, the difficulty of capturing the costs associated with using private services or purchasing equipment within metrics such as QALYs was highlighted by a professional expert submission.

In terms of services associated with administering nusinersen and risdiplam, some patient expert submissions noted that there is a higher cost associated with nusinersen treatment due to the need for lumbar punctures every four months. They highlighted the need for facilities to be able to conduct the procedure, including radiology or CT scans were needed. By contrast, one patient expert submission (adult with SMA) noted that risdiplam would have less impact on the NHS because it is administered at home. However, a professional group submission also noted that specialist pharmacy knowledge and dispensing was required when prescribing risdiplam, implying a greater level of training needed to dispense the treatment. Members of patient groups who spoke with the EAG noted that, despite the costs associated with nusinersen compared with risdiplam, it was important to consider patient choice and the accessibility of both treatment options. As previously noted, a professional expert submission also highlighted that adverse events or no perceived benefits may be reasons for people to switch treatments. Furthermore, Association of British Neurologists noted that if both treatments were available outside of the current MAA, the need for monitoring in the adult population could be reduced from every 6 to every 12 months, given that motor function appears to stabilise and “no blood abnormalities have been detected”.

15.4 Summary of cost-effectiveness results

The EAG assessed the cost-effectiveness of nusinersen and risdiplam in the treatment of people with presymptomatic SMA, type 1 SMA and types 2/3 SMA. The differences in patient characteristics for nusinersen and risdiplam meant that cost-effectiveness of these DMTs were assessed by making changes to Biogen’s and Roche’s base-case models, respectively (see Section 12.2). The cost-effectiveness results should also be read in the context of the qualitative analyses (see Section 13.5), as well as specific qualitative analyses surrounding economic considerations (see Section 15.3).

15.4.1 Presymptomatic population

The EAG’s base-case analysis for nusinersen compared to BSC using the economic evidence provided by Biogen showed that [REDACTED]

[REDACTED] compared to BSC. Both the deterministic and probabilistic results were consistent, where nusinersen had a [REDACTED] probability of being cost-effective. Results closely aligned with Biogen’s base-case economic analysis. Disease-related costs of “not sitting”, “sitting without support” and “permanent ventilation” had the largest

impact on the results. Scenarios with the most impact were using health-state costs from TA588² and TA755³. The scenario analysis comparing nusinersen with OA showed that

The EAG's base-case analysis for risdiplam compared to BSC using the economic evidence provided by Roche showed that risdiplam was

. Parameters with the biggest impact on the ICER compared to BSC were the drug price of risdiplam, disease related costs for children at the "not sitting" and "sitting" health-states, the risk of permanent ventilation and disease-related costs for adults at "not sitting" and "walking" health states. Scenarios with the biggest impact on the ICER were the choice of time horizon, using health-state costs from TA588² and TA755³, and adding carer utilities.

The scenario analysis comparing risdiplam with nusinersen, assuming equivalent effectiveness, showed . Comparing risdiplam with nusinersen using the naïve comparison showed . The scenario analysis comparing risdiplam with OA assuming equivalent effectiveness showed .

15.4.2 Type 1 SMA

The EAG's base-case analysis for nusinersen compared to BSC using the economic evidence provided by Biogen showed that

. The probabilistic analysis showed similar results to the base-case, indicating probability of nusinersen being cost-effective compared with BSC. Parameters with the biggest impact on the ICER were health-state utilities and health-state costs for "permanent ventilation", "not sitting" and "sitting without support," respectively. Scenarios with the largest impact were using health-state utilities from TA755³ and using health-state related costs from TA588² and TA755³.

²⁶² The scenario comparing nusinersen with OA showed

The EAG's base-case analysis for risdiplam compared to BSC using the economic evidence provided by Roche showed that risdiplam was

. Parameters with the biggest impact on the ICER compared to BSC were the overall survival benefit of risdiplam, the drug cost of risdiplam, patient disease-related costs and disease-related utilities at "sitting", as well as the benefit surrounding risk of permanent ventilation. The scenario analysis between risdiplam and BSC showed that scenarios with the biggest impact on the ICER were using the utilities from the Roche base-case analysis (based on TA755³), changing the length of the time horizon, and pooling patient

and carer utilities.
 [REDACTED]
 [REDACTED].

The scenario comparing risdiplam with nusinersen in type 1 patients showed [REDACTED]. The scenario comparing risdiplam with OA showed [REDACTED].

15.4.3 Type 2/3 SMA

The EAG's base-case analysis for nusinersen compared to BSC using the economic evidence provided by Biogen showed that [REDACTED]. The probabilistic analysis showed similar results to the base-case, [REDACTED]. Parameters with the biggest impact on the ICER compared to BSC were disease-related health-state costs for "sitting without support" and "not sitting", as well as disease-related health-state utilities. Scenarios with the largest impact on the ICER were including carer utilities, using patient utility estimates from TA755³, using patient utility estimates from the SUNFISH trial, and using health-state costs from TA755³ and TA588². Subgroup analyses for type 2 and type 3, run separately, led to [REDACTED]. Assuming a £0 price for nusinersen would make nusinersen [REDACTED] for the type 2/3 SMA population.

The EAG's base-case analysis for risdiplam compared to BSC using the economic evidence provided by Roche showed [REDACTED]. Parameters with the biggest impact on the ICER compared to BSC were the drug cost of risdiplam, disease-related costs at "not sitting" and "sitting without support" for adults, and utilities for "sitting without support". Scenarios with the largest impact on the ICER were using patient disease-related health-state utilities from the Roche base-case (sourced from Lloyd et al⁶⁷) or from the SUNFISH⁴⁷ trial, shortening the time horizon, using patient and carer utilities, and using disease-related health-state costs from the Roche base-case.

The scenario comparing risdiplam with nusinersen in type 2 and 3 patients showed that risdiplam was [REDACTED] than nusinersen, [REDACTED].

15.5 Key issues in the models and cost-effectiveness results

The EAG note that there were several key issues surrounding the modelling of cost-effectiveness for nusinersen and risdiplam. Firstly, the effectiveness data (e.g. transitions, relative effect, decline in health states) used in the cost-effectiveness models largely come from single arm trials in the absence of RCTs. Whilst it may not be always feasible or ethical to conduct a RCT for treatments in rare diseases like 5q SMA, therefore making it necessary to use the effectiveness data derived from single arm trials. However, using evidence from single arm trials may introduce bias in favour of the treatments under evaluation.

The motor milestone scores used in defining the disease progression in terms of model health states are derived from different tools which vary in their scoring system. The EAG notes that assuming equivalence between health states defined by these differing tools may introduce uncertainties around motor functions, patient health states and, ultimately, in the cost-effectiveness results.

The utility scores used for each model's health states may not adequately capture the nuanced motor improvements from treatments that are meaningful to SMA patients, as well as their families and carers (e.g. lifting the head, holding objects, or sitting independently for a few seconds). These smaller but important improvements in fine motor functions highlighted in the qualitative analyses from discussions between the EAG and professional and patient organisations. To reflect these benefits, a utility increment of 0.1 was assumed and incorporated into the economic models. However, the EAG cautions that this utility increment may not fully or accurately represent the true value of these additional improvements.

The EAG's base-case models did not explicitly incorporate the utility and costs impacts of bulbar function, non-ventilatory respiratory support and scoliosis separately. These impacts were assumed to be captured within the HSUVs and associated resource utilisation costs. The EAG was concerned that including these elements separately could result in double counting of their impact on cost-effectiveness. However, based on input from the clinical experts and patient organisations, the EAG recognises the particular importance of maintaining or improving bulbar function for people with SMA (see Section 13.5.11). In response, the EAG conducted a scenario analysis within type 2/3 model, incorporating both utility decrement and additional healthcare costs associated with bulbar function. Due to a lack of relevant data, it was not possible to model the impact of bulbar function for presymptomatic or type 1 populations. Even within the type 2/3 model, the data used to inform the bulbar dysfunction were limited and several assumptions were required. Therefore, the results of this scenario analysis should be interpreted with caution.

Carer utility increments were not incorporated in the EAG's base-case models because of concerns regarding the methodological approaches used and the robustness of the underlying evidence. There are a significant number of issues to appropriately incorporate carer utilities into the analysis requiring lots of assumptions which introduce uncertainty. Some of these assumptions include whether carer utilities vary according to the age of the person cared for, whether they vary according to the functional state in addition to the SMA type the person cared for is in, what the characteristics of the carer are (i.e starting age, sex, impact on their health and life-expectancy) in order to estimate utility scores, how long the carer can provide care for and what would happen if they were no longer able to provide care. This clearly needs significant thought and data collection to capture and incorporate in a meaningful manner. Nonetheless, qualitative discussions with patient organisations highlighted the significant financial, physical, psychological and social burdens experienced by those caring for individuals with SMA, and should not be undermined (see Sections 13.5 and 15.3). While the exclusion of carer utility gains from the EAG's base-case analysis may have understated the full value of treatments, the impact of incorporating, in a limited manner, carer utility in the cost-effectiveness results was explored through the scenario analyses to show the potential impact.

Discontinuations from treatments were informed by the MAA data but was incorporated only into the nusinersen model. Roche did not include treatment discontinuations in their model, reasoning that discontinuation from risdiplam was unlikely or impractical - however this

assumption may have favoured risdiplam as the EAG's discussions with clinical experts suggested that people may discontinue or switch from risdiplam due to known adverse events, such as potential effects on fertility. The EAG also notes that the discontinuation data used in the models were based on short-term MAA follow-up, which may have overestimated the sustained benefits from treatments over the patient's lifetime. In addition, discontinuations from nusinersen incorporated into the Biogen model assume that patients discontinuing treatments would go onto receive BSC, accruing the costs and outcomes of BSC after discontinuation. However, in clinical practice, those discontinuing may switch to alternative DMTs rather than BSC alone. Due to the lack of robust evidence, the potential impact of treatment switching could not be modelled. The EAG therefore, cautions that assumptions surrounding treatment discontinuations may introduce additional uncertainty into the cost-effectiveness results.

Furthermore, in the scenario analysis comparing nusinersen with OA using the presymptomatic and type 1 models, the EAG assumed equal effectiveness between the two treatments. This assumption may be inaccurate and could potentially favour one treatment over the other. To address this, a scenario analysis was conducted assuming non-equivalence, based on state occupancy data derived using the unanchored MAIC. However, due to the limited robustness of the unanchored MAIC data, any conclusions drawn from this analysis should be interpreted with caution.

Overall, the cost-effectiveness results are largely based on limited evidence and should be interpreted with caution. In the absence of robust comparative data, the EAG concludes that there is insufficient evidence to accurately estimate the relative net health benefits of risdiplam or nusinersen in patients with SMA.

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16 Discussion

16.1 Statement of principle findings

16.1.1 Qualitative

Overall, the qualitative framework analysis highlighted the great impacts of living with SMA, not just on individuals' functional status (e.g. motor function) but also on their ability to socialise and interact with others, activities of daily living (e.g. being able to eat, wash and clothe themselves independently), and overall quality of life. The analysis also highlighted the personal financial implications of SMA on patients and their families and carers, such as the need to buy specialist equipment to facilitate daily living. Although motor function was often mentioned by people within the qualitative analyses, the data also suggested that treatments for SMA can improve bulbar and respiratory function, which in turn improves overall quality of life and people's ability to perform daily activities. Potential adverse events of either nusinersen or risdiplam were less frequently mentioned within the qualitative data.

In discussion with the EAG, it was also stated by professionals and representatives of patient organisations that outcomes such as bulbar function and stamina or fatigue were highly important to people with SMA but that data on these outcomes were less frequently captured and reported within the current evidence base; this was true of the current updated SLR. Furthermore, the qualitative analysis highlighted that the current tools used to measure motor function, of which the bulk of the quantitative analysis in the SLR focuses, are not sensitive enough to capture important maintenance and improvements in fine motor skills (e.g. being able to independently use cutlery or a wheelchair).

16.1.2 Clinical effectiveness

Motor function: In the controlled and uncontrolled evidence for both nusinersen and risdiplam, maintenance or improvement in assessed motor functions were generally reported. This was coupled with little evidence of deterioration. This is true for all types of SMA included in the report (presymptomatic, type 1, type 2/3).

Bulbar function: For nusinersen, the evidence across the SMA types suggested there was a reduction in the need for nutritional support. This was demonstrated by improvement or stability in ability to swallow, maintenance of eating function and a reduced need for gastrostomy or nasogastric tube feeding indicating overall enhancement in bulbar functions. However, there is evidence for increased need for nasogastric tube feeding in a few studies, especially those with multiple and unreported type SMA. Additionally, treated patients maintained their swallowing functions, most notably amongst SMA type 1 patients. Furthermore, there was consistent evidence of reduced need for speech therapy among participants receiving nusinersen treatment, particularly those who adhered closely to the regimen. Importantly, there was no evidence for deterioration in cry function among the patients. For risdiplam, there was similar evidence for presymptomatic and type 1 patients, with both either maintaining or improving their bulbar function. In type 1 patients there were observed increases in the number of patients able to feed orally.

Hospitalisation: Data was limited for both treatments. Risdiplam was shown, in a single study, to reduce hospitalisation rates per person year to 0.7, compared to a natural history range of 4.2 and 7.6 every year, in type 1 patients. Nusinersen reportedly had rates of 4.5 per patient year, which was higher than OA treated type 1 patients. Although hospitalisation data

for nusinersen were limited, lower SAE rates in treatment groups suggest a stabilising effect on disease progression, with potential implications for reduced hospital-based care.

Respiratory function: For risdiplam there was a general maintenance of respiratory functions among patients especially in FVC maintenance and a phase reduction in respiratory plethysmography. Additionally, no patients required ventilatory support across all SMA types. There was evidence for improved or preserved respiratory functions in most assessments across all SMA types. Notably, nusinersen-treated patients demonstrated preserved respiratory function, with no progression to permanent ventilation reported across multiple cohorts.

Complications: While complications in later-onset SMA—such as respiratory infections and scoliosis—were reported, they were generally manageable and not directly attributed to the drugs. In some cases, these complications may reflect disease progression or, to a lesser extent, the method of treatment administration, underscoring the importance of integrated, multidisciplinary long-term care, including orthopaedic and rehabilitative support.

Fatigue and stamina: For nusinersen there were mixed outcomes for fatigue and stamina especially with two studies among mixed type SMA showing improvement in fatigue showed whilst one noted increased fatigue. There was no available evidence for this outcome assessing risdiplam treatment.

Mortality: For both drugs mortality was generally low. Both drugs were particularly impactful for type 1 patients, where natural history median life expectancy is 10 months; however 75% of patients were still alive on nusinersen after three years and 91% of patients on risdiplam after five years. Most deaths were attributed to SMA-related complications. Findings support a durable survival benefit across both infantile- and later-onset SMA, particularly with early initiation.

Adverse events: Across SMA types, both nusinersen and risdiplam demonstrated favourable long-term safety profiles, with most AEs reported as mild to moderate in severity and declining in frequency over time. SAEs were more frequently observed in control groups, and treatment discontinuation remained rare for both therapies. Long-term data consistently reinforced the tolerability and durability of clinical benefit, with no new safety signals emerging across trials.

PROMs and QoL: For nusinersen and risdiplam limited evidence was found by the SLR regarding PROMs and QoL outcomes, which were highlighted as key outcomes by the patient and professional groups. Further work is necessary here to understand the impact on patients' and carers' QoL following treatment.

Nusinersen and risdiplam (comparative evidence): A single study directly compared the efficacy of nusinersen and risdiplam in a prospective cohort. This study further highlighted the differences in populations for the two treatments, with statistically significant differences for baseline characteristics including motor function outcomes, therefore supporting the view that ITC is likely inappropriate. Both nusinersen and risdiplam showed statistically significant improvements in motor function from baseline to 6 months. However, no statistically significant difference was observed between the two treatments. Another study was identified but the results were reported as a combination of disease modifying treatments (OA, nusinersen, and risdiplam); inferences for the individual treatments were therefore not possible.

MAA: The MAA data showed evidence of maintenance or improvement mostly for motor outcomes, across all types, for both nusinersen and risdiplam. For the paediatric registry,

nusinersen had a longer follow-up data available than risdiplam (~4+ years vs ~1.5+ years, respectively) for motor outcomes. While the adult registry for risdiplam did extend to ~4 years, the patient numbers were smaller at this point than those in the nusinersen MAA. This is to be expected given the timelines of when each drug was made available, with nusinersen being made available first. The PROMS outcomes lack data, with some varying results but maintenance or improvement was reported for some scales. Similarly, the QoL results are lacking in data but do show some improvement. Importantly, mortality rates in the MAA were generally low for both treatments, and deaths that did occur appeared to not be related to treatments.

Overall, these findings support the ongoing use of both agents as safe, well-tolerated, and clinically effective options in the long-term management of SMA. However, while clinical effectiveness is evident—particularly in comparison to control groups—cost-effectiveness assessments may be less favourable, especially when compared with single-dose gene therapies. This highlights the need for continued economic evaluation and prioritisation within healthcare decision-making frameworks.

16.1.3 Cost-effectiveness

Differences in the eligible populations for nusinersen and risdiplam, reflected in the very limited comparative data and the robustness of indirect treatment comparisons and the associated MAICs, meant that the EAG did not consider it appropriate to combine the assessment of the two therapies in a single model. The EAG's base-case analysis therefore focused on evaluating nusinersen and risdiplam independently. Each treatment was compared separately against best supportive care (BSC), rather than directly against one another or against OA.

16.1.3.1 Cost-effectiveness analysis for nusinersen

Presymptomatic

Biogen compared nusinersen only with BSC for the presymptomatic population justifying this approach on the basis that there was insufficient evidence to support a reliable comparison between nusinersen and risdiplam or OA. The economic model structure in the Biogen submission focused on a set of motor-milestone gains and losses defined by the WHO-MM instrument and categorised as “not sitting”, “sitting without support”, “standing with support”, “walking independently”. The presymptomatic and type 1 models also included the risk of moving from “not sitting” to “permanent ventilation”. While this focus on a defined set of motor milestones was a pragmatic approach given the available evidence, patients and clinical expert raised concerns that some of the instruments used may not capture all relevant aspects of the disease progression or treatment benefit, particularly more subtle changes in mobility.

For the presymptomatic population, Biogen used data from the NURTURE,^{30,34} a single-arm study and conducted a naïve comparison against BSC using data from the control arms in ENDEAR²⁷ and CHERISH²⁸ for motor milestones. Due to a lack of events, survival assumptions in this model were informed by the most recent NICE appraisal in this area (HST24¹⁶).

Patient health-related quality of life (HRQoL) data were not collected from NURTURE nor ENDEAR, instead, the model adopted the approach to patient HRQoL from HST24¹⁶ and

applied it to the presymptomatic, type 1, and type 2 and 3 population models. The EAG noted there were large uncertainties in the utility estimates used to calculate patient HRQoL, particularly around the most severe health-states of “permanent ventilation” and “not sitting” given the methodological difficulties of measuring HRQoL on children, the severity, and the rarity of the condition.

The base-case analysis from Biogen pooled together the HRQoL of informal carers and patients using estimates from the literature and the approach from TA755³. As the base-case approach combined patient and carer HRQoL, a severity modifier was not applied to the results. The EAG raises concern that carer HRQoL data were not collected from the clinical studies but instead were derived from a previous NICE appraisal. Additionally, the EAG highlights there was a lack of standardisation in the methods for including informal carer HRQoL. The EAG recognises that the perspective from informal carers is relevant and an important dimension in SMA and NICE methods guidelines supports its inclusion; therefore the EAG conducted a scenario analysis pooling patient and carer HRQoL, assuming on average a single carer per patient and using more recent HRQoL estimates from Lo et al.⁷¹ Considering the limitations in the evidence, the EAG considered it more appropriate to focus the base-case analysis on patient HRQoL alone as a better reflection of disease severity, moreover this approach also aligns with previous appraisals on this area.^{244,253}

The Biogen model applied health care cost estimates from the recent NICE appraisal in this area (HST24¹⁶) across presymptomatic, type 1, and type 2/3 models. The EAG noted large variation in disease-related costs estimates across previous NICE appraisals (HST24¹⁶ TA755³). While the EAG considers the estimates from the latest appraisal to be appropriate, it also acknowledges uncertainties around costs for “permanent ventilation”, “not sitting”, and “sitting without support” which can substantially influence the cost-effectiveness results.

The approach to modelling the disease included a long-term risk of motor-milestone decline beginning after [REDACTED] for patients receiving nusinersen, and 15 months for BSC based on the evidence available from the clinical trials and the literature. Additionally, patients receiving nusinersen were also at risk of discontinuing after which they moved to BSC, an assumption based on discontinuation observed in the trials.

Cost-effectiveness results from Biogen showed

[REDACTED]

[REDACTED]. Parameters with the largest impact on cost-effectiveness as expected were disease-related costs estimates at “sitting without support”, “not sitting”, and “permanent ventilation”.

The EAG analysis updated costs and mortality estimates to the most recent values, assumed a 10% increase in patient utility from treatment, and focused on patient HRQoL and meeting the criteria for the severity modifiers. The EAG also explored a scenario comparing nusinersen with OA using the evidence provided by Biogen. The EAG’s base-case analysis comparing nusinersen to BSC resulted in nusinersen being [REDACTED] and had [REDACTED] probability of being cost-effective. Uncertainty around estimates of disease-related costs above also impacted the EAG’s results. The scenario analysis comparing nusinersen with OA showed that nusinersen was [REDACTED] and [REDACTED] than OA, [REDACTED].

Type 1

For type 1, Biogen compared nusinersen only with BSC, justifying that it was not appropriate to assess the relative effectiveness of nusinersen against risdiplam or OA, given the gaps in the relative effectiveness evidence available. The economic model structure in the Biogen submission followed the same structure as the presymptomatic population.

For the type 1 population, Biogen used data from the ENDEAR²⁷-SHINE³⁵ controlled trial and its extension, which informed transitions in motor-milestones, risk of death and risk of permanent ventilation for both nusinersen and BSC.

[REDACTED]

The approach to incorporate patient and informal health-related quality of life (HRQoL) in the type 1 model followed the same assumptions used in the presymptomatic model, therefore the same critiques apply to type 1 population. The approach to include disease-related health care costs in type 1 model was same as that of the presymptomatic model, however the EAG considers the concerns around the lack of robust evidence for costs in severe disease health states to be even more critical for type 1 population.

The approach to modelling the disease included a long-term risk of motor-milestone decline after [REDACTED] for nusinersen, and 15 months for BSC based on the evidence available from ENDEAR²⁷ and the literature. Patients receiving nusinersen were also at risk of discontinuing and moving to BSC based on evidence from the trials.

Cost-effectiveness results from Biogen showed that nusinersen compared to BSC [REDACTED]. Parameters with the largest impact the company base-case were disease-related patient utility values (although the model could not present the impact of utility values for each health-state), and the costs at “permanent ventilation”, “sitting without support” and “not sitting”.

[REDACTED]

The EAG analysis updated costs and mortality estimates to the most recent values, assumed a 10% increase in patient utility from treatment, and focused on patient HRQoL and meeting the criteria for the severity modifiers. The EAG also explored a scenario comparing nusinersen with OA using the evidence provided by Biogen. The EAG’s base-case analysis comparing nusinersen to BSC showed that

[REDACTED]. The scenario comparing nusinersen with OA showed [REDACTED].

Type 2/3

For type 2/3, Biogen compared nusinersen only with BSC justifying that it was not appropriate to assess the relative effectiveness of nusinersen against risdiplam, given the gaps in the

relative effectiveness evidence available. The economic model structure in the Biogen submission³¹ included the same motor-milestone health states as those used in the presymptomatic and type 1 models. However, unlike the previous models type 2/3 model did not include a transition from “not sitting” to “permanent ventilation” reflecting the disease progression for type 2/3 population.

For the type 2/3 population, data were drawn from the CHERISH²⁸-SHINE³⁵ controlled trial and extension study to inform motor milestone transitions for both nusinersen and BSC. Due to a lack of events, survival assumptions in this model were informed by the approach in the previous NICE submission HST24¹⁶, and general UK population survival. [REDACTED]

The approach to include patient and informal health-related quality of life (HRQoL) followed the same assumptions as the presymptomatic and type 1 models, therefore the same critiques apply. The approach to include disease-related health care costs from the presymptomatic model was also followed for the type 1, and type 2/3 models with the same concerns regarding the high variance and lack of evidence supporting estimates of disease-related costs. After consultations with patients and clinical experts, bulbar function was featured as a key concern for patients for which there was little evidence of treatment effect from the clinical studies. The EAG included a scenario analysis explicitly modelling the impact of bulbar dysfunction as a reduction in patient HRQoL, but due to the paucity of evidence we could not inform the base-case analysis. The evidence considered to explore the impact of bulbar dysfunctions was drawn from the Roche submission⁴⁴ and involved applying disutilities and additional costs on an assumed proportion of patients in each health state (excluding death). Nevertheless, the EAG cautions that these data may not accurately reflect the characteristics of patients treated with nusinersen.

The approach to modelling the disease included a long-term risk of motor-milestone decline after [REDACTED] for nusinersen, and 15 months for BSC based on the evidence available from CHERISH²⁸ and the literature. Patients receiving nusinersen were also at risk of discontinuing and moving to BSC based on evidence from the trials.

Cost-effectiveness results from Biogen showed that [REDACTED].

Parameters with the largest impact on results were the carer and patient utility values, and disease-related costs at “sitting without support” and “not sitting”.

The EAG analysis updated costs and mortality estimates to the most recent values, assumed a 10% increase in patient utility from treatment, and focused on patient HRQoL and meeting the criteria for the severity modifiers. The EAG also presented alternative scenarios using patient HRQoL from the Roche submission, patient HRQoL from the SUNFISH⁴⁷ trial, and the inclusion of bulbar function based on data from the Roche type 2/3 submission⁴⁴. The EAG's base-case analysis for nusinersen compared to BSC showed [REDACTED]

[REDACTED]. Scenarios with the largest impact on results were including the impact on carer HRQoL, changing the patient utility estimates to those in the Roche type 2/3 model, or using utility estimates from the SUNFISH⁴⁷ trial, [REDACTED].

16.1.3.2 Cost-effectiveness analysis for risdiplam

Presymptomatic

For the presymptomatic population, Roche compared risdiplam with nusinersen and OA. BSC was considered inappropriate comparator in this population, as it is rarely used in clinical practice for presymptomatic patients. The economic model structure used in the Roche submission was based on TA755³ and defined health states focused on a set of motor milestone gains and losses measured by the HINE-2 instrument. These health states were categorised as “not sitting”, “sitting with or without support”, “standing with or without support”, and “walking with or without support”. The presymptomatic and type 1 models also included the risk of moving from “not sitting” to “permanent ventilation”. While focusing on this set of motor milestones was a pragmatic approach aligned with the available the trial evidence, the patients and clinical experts raised concerns that some of the instruments used may place too much emphasis on certain aspects of disease, and they may overlook other meaningful changes in mobility and other broader treatment benefits.

For the presymptomatic population, Roche used data from the RAINBOWFISH⁵⁷ single-arm study and assumed equivalent effectiveness across risdiplam, nusinersen and OA, based on result of a naïve comparison with NURTURE³⁰ and SPR1NT studies.⁴⁴ Although the model included data for BSC derived from an internal, unpublished natural history study, Roche did not consider the BSC to be a relevant comparator in the decision problem as it would be quite rare in clinical for presymptomatic population not to be treated.

While the EAG acknowledges that BSC does not represent current clinical practice in the presymptomatic population; it also highlights important gaps in the relative effectiveness evidence between risdiplam and other disease modifying therapies. Therefore, from an analytical perspective, the EAG opted to include a comparison of the cost-effectiveness of risdiplam relative to the absence of risdiplam in BSC, assuming the natural history of disease progression provided by Roche for the presymptomatic model.

The Roche model assumed long-term maintenance or improvement of motor milestones after 120 months for risdiplam, nusinersen, and OA, with no risk of treatment discontinuation for patients receiving risdiplam. However, the EAG considered that this assumption may overestimate long-term benefits of risdiplam, especially given the lack of long-term follow-up data from clinical trials. Therefore, in order to improve consistency between the economic models submitted for this appraisal the EAG adopted the approach used in Biogen model and assumed a long-term risk of either maintaining or losing motor milestones after 72 months for risdiplam and 12 months for BSC, based on available trial evidence and supporting literature. The EAG acknowledges this may be a conservative assumption, particularly if further evidence demonstrates sustained motor milestones with the disease modifying therapy. Nevertheless, the EAG considers this approach of assuming long-term risk of maintaining or losing motor milestones more appropriate given the uncertainty around long-term data.

In the absence of an appropriate estimate for treatment related discontinuation with risdiplam, the EAG retained the assumption of no discontinuations for risdiplam (and for nusinersen in the scenario analysis) in the Roche model. However, the EAG acknowledges that this is a favourable assumption for the disease modifying therapy as it may overestimate the long-term treatment benefits, particularly given the clinical expert opinion that some patients may discontinue because of adverse events or issues related to fertility.

Patient health-related quality of life (HRQoL) data was not collected from either RAINBOWFISH⁵⁷ or FIREFISH.⁵⁶ Instead, the model adopted the approach to patient HRQoL from TA755³ and applied it through the presymptomatic and type 1 population models. The EAG noted there were large uncertainties in the utility estimates used to calculate patient HRQoL, particularly around the most severe health-states of permanent ventilation and “not sitting”, given the methodological difficulties of measuring HRQoL on children, the severity, and the rarity of the condition.

The EAG also noted the presence of negative utility values at the permanent ventilation state in the Roche base-case approach. There was a general concern about utility at this stage as utility values were anchored at death equivalent to 0, therefore gains in survival at the permanent ventilation state would count against any intervention. We consulted a clinician who showed further concern for this assumption around negative utilities at permanent ventilation. The approach adopted by the EAG based on HST24¹⁶ assumed a utility of 0 at permanent ventilation, which is still a cause of concern but does not punish improvements in survival at this health-state. While the EAG also explored alternative scenarios with different patient utility values, any negative utilities were always assumed to be equal to 0 in our analyses.

The Roche model added separately the impact and costs of bulbar dysfunction, severe scoliosis, and non-permanent respiratory support on BSC using estimates from an internal, unpublished, natural history of disease study. The EAG was concerned this approach resulted in double-counting the disease-related burden in patient HRQoL in BSC, as the impact of disease-related events is likely to be included in HRQoL estimates of the disease. Moreover, there was a lack of evidence from the clinical studies around the impact of risdiplam on these disease-related events relative to BSC. Therefore, the EAG opted to exclude the added impact on these disease-related events in the base-case analysis.

The base-case analysis pooled together patient and informal care HRQoL based on an approach used in TA755.³ As the base-case approach combined patient and carer HRQoL, a severity modifier should not have been applied to the results. The EAG express concern that evidence on informal carers came from a previous NICE appraisal rather than being collected in the clinical studies; at the same time there was a lack of standardisation in the methods for including informal carer HRQoL, with important differences in the approaches employed by Biogen and Roche regarding numbers of carers and the conceptualisation of the carer burden.

The EAG acknowledges that the perspective of informal carers is an important consideration in SMA and, given that the NICE methods guidelines support the inclusion of the carer HRQoL, the EAG conducted a scenario analysis that pooled together the patient and carer HRQoL, assuming on average, a one informal carer per patient and using HRQoL estimates from a more recent study by Lo et al.⁷¹ However, given the limitations in the evidence available, the EAG opted to focus the base-case analysis on patient HRQoL alone as a more appropriate approach to represent the severity of the disease, moreover this approach aligns with that taken in previous appraisals on this area.^{244,255}

Roche’s submission used an expert elicitation exercise conducted by the company to inform NHS-related and personal social services costs across patients with type 1, type 2, and type 3 SMA. Costs for presymptomatic patients were assumed to be equivalent to type 1 patients. The EAG noted considerable variation in disease-related costs estimates used in the Roche model and those from previous NICE appraisals (e.g. HST24¹⁶ and TA755³), and the EAG considered estimates from the recent NICE appraisal (HST24¹⁶) were appropriate. However,

there significant uncertainties remain around costs for “permanent ventilation”, “not sitting”, and “sitting with or without support”, all of which have a substantial impact on the cost-effectiveness of the treatment.

Cost-effectiveness results from Roche showed that including carer and patient HRQoL risdiplam

For the comparison between risdiplam and BSC parameters with the biggest impacts on results were drug related costs for risdiplam, disease-related costs for children at “sitting” and “not sitting” health states, and patient and carer utilities at “walking”.

The EAG changed the time horizon from [REDACTED] in the Roche base-case to 100 years, as risk improvements in survival from treatment beyond the initial time horizon would not be accounted for as well as treatment-related resource use. Only a small proportion of patients are expected to reach the end of our time-horizon, making sure that we captured all relevant health benefits and costs.

The EAG analysis incorporated updated costs and mortality estimates to the most recent data, assumed a 10% increase in patient utility from treatment, and focused on patient HRQoL and ensuring alignment with the criteria for the severity modifier. Our base-case analysis focused on risdiplam and BSC, with scenario analyses comparing risdiplam and nusinersen, and risdiplam and OA using the available evidence provided by Roche. Due to the lack of survival data in the trial, survival assumptions followed the approach from HST24.¹⁶

The EAG's base-case results showed that risdiplam compared to BSC [REDACTED]. Results were highly sensitive to the drug price of risdiplam, disease-related costs for children at the “not sitting” and “sitting” health-states, the risk of permanent ventilation and disease-related costs for adults at “not sitting” and “walking” health states. The scenario analysis comparing risdiplam with nusinersen, assuming equivalent effectiveness [REDACTED]. Comparing risdiplam with nusinersen using the naïve comparison showed [REDACTED]. The scenario analysis comparing risdiplam with OA assuming equivalent effectiveness [REDACTED].

Type 1

For type 1, risdiplam was compared with nusinersen, OA, and BSC. The economic model structure in the Biogen submission followed the same structure as the presymptomatic population.

For the type 1 population, Roche used data from the FIREFISH⁵⁶ trial, a single-arm trial for risdiplam, and applied the estimates from the unanchored MAIC with ENDEAR²⁷ to estimate the relative effectiveness of nusinersen and BSC, as well as STR1VE-EU⁶⁵ for OA. These data informed model transitions for motor milestones, overall survival, and the risk of death or

permanent ventilation (from EFS data).

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. In line with our concerns with the quality around the relative efficacy data available, the EAG's base-case analysis focused on comparing risdiplam with BSC, but this meant using the unanchored MAIC results between FIREFISH⁵⁶ and ENDEAR²⁷ as the best available evidence. The EAG also presented scenario analyses using the evidence from Roche to compare risdiplam and nusinersen, and risdiplam and OA.

The Roche model assumed long-term maintenance or improvement of motor milestones after 66 months for risdiplam, nusinersen, and OA, with no risk of treatment discontinuation for patients receiving risdiplam. The EAG challenged this assumption in the presymptomatic model and adopted the approach to modelling long-term risk of decline from the Biogen submission using estimates from the published MAIC results in Ribero et al. 2022.⁶⁴ This approach assumed that risk of maintenance of decline starts after 60 months for risdiplam and 12 months for BSC. The assumption of no discontinuation for risdiplam and nusinersen was maintained in the type 1 model, the concerns of favouring these disease-modifying therapies presented for the presymptomatic model also applied here.

Patient HRQoL data was not collected from either RAINBOWFISH⁵⁷ or FIREFISH.⁵⁶ Instead, the model adopted the approach to patient HRQoL from TA755³ and applied it through the presymptomatic and type 1 population models. For consistency, patient utilities from HST24¹⁶ were applied across the presymptomatic, type 1, and type 2/3 models. Our concerns around negative utilities from the presymptomatic model still applied here.

The Roche model added separately the impact and costs of bulbar dysfunction, severe scoliosis, and non-permanent respiratory support on risdiplam and BSC using estimates from the literature. The EAG was concerned about the appropriateness of this approach given the risk of double-counting the impact of disease-related events, and the gap in the evidence regarding the impact of disease-modifying therapies in this area, therefore these were excluded from the base-case analysis. The approach to incorporate carer utilities was the same for presymptomatic, type 1, and type 2/3 patients, therefore our concerns still applied here. The approach to include disease-related health care costs in type 1 model was same as that of the presymptomatic model, however the EAG considers the concerns around the lack of robust evidence for costs in severe disease health states to be even more critical for type 1 population.

Cost-effectiveness results from Roche showed that including carer and patient HRQoL risdiplam compared to BSC. Results were sensitive to estimated overall survival improvements, estimated permanent ventilation risk improvements, and the cost of risdiplam.

The EAG analysis incorporated updated costs and mortality estimates to the most recent data, assumed a 10% increase in patient utility from treatment, and focused on patient HRQoL and ensuring alignment with the criteria for the severity modifier. The EAG also changed the time horizon from in the Roche base-case to 100 years, as risk improvements in survival from treatment beyond the initial time horizon would not be accounted for as well as treatment-related resource use. Only a small proportion of patients are expected to reach the end of our time-horizon, making sure that we captured all relevant health benefits and costs. Our base-case analysis focused on risdiplam and BSC, with scenario analyses comparing risdiplam and nusinersen, and risdiplam and OA using published evidence from Ribero et al. 2022.⁶⁴

The EAG's base-case analysis for risdiplam compared to BSC

[REDACTED]. Results were sensitive to the overall survival benefit of risdiplam, the drug cost of risdiplam, patient disease-related costs and disease-related utilities at "sitting with or without support", as well as the risk of permanent ventilation. Assuming a drug price of £0 for risdiplam still led to risdiplam being above the £30,000/QALY threshold, showing there is a potential that, due to the high costs between "not sitting" and "sitting with or without support", risdiplam as a therapy was not cost-effective at £0.²⁶² The scenario analysis comparing risdiplam with nusinersen showed that risdiplam was [REDACTED] than nusinersen, [REDACTED]. The scenario analysis comparing risdiplam with OA showed that risdiplam was [REDACTED] than OA, [REDACTED].

Type 2/3

For the type 2/3 model in the Roche submission, risdiplam was compared with nusinersen and with BSC. The economic model structure used in the Roche submission was based on TA755³ and defined health states focused on a set of motor milestone gains and losses measured by the MFM-32 and the HFMSE instruments. These health states were categorised as "not sitting", "sitting with support", "sitting without support", "standing (with or without support)", and "walking (with or without support)".

Data was sourced from the SUNFISH⁵³ study, a controlled trial informing transitions between motor milestones for nusinersen and BSC. Due to a lack of events, survival assumptions were informed by pooled survival data from published studies identified in the literature review for type 2 patients, and general population survival for type 3 patients, and an assumption of lower overall [REDACTED] survival for BSC.

[REDACTED]⁵³

[REDACTED]. Given the absence in survival evidence and for consistency with the previous economic models the EAG followed the survival assumptions from HST24¹⁶, where survival gains are a result of improvements in mobility and not directly influenced by treatment in the type 2 and 3 population.

The Roche model assumed long-term maintenance or improvement of motor milestones after 60 months for risdiplam and nusinersen, with no risk of treatment discontinuation for patients receiving risdiplam or nusinersen. The EAG challenged this assumption in the presymptomatic model and adopted the approach to modelling long-term risk of decline from the Biogen submission using published estimates from SUNFISH in Oskoui et al. 2023.⁵¹ This approach assumed that risk of maintenance of decline starts after 96 months for risdiplam and 12 months for BSC. The assumption of no discontinuation for risdiplam and nusinersen was maintained in the type 2/3 model, the concerns of favouring these disease-modifying therapies presented for the presymptomatic model also applied here.

Patient EQ-5D data was collected from SUNFISH⁵³, but the estimates were not validated by experts. Instead, the model adopted the approach to patient HRQoL from Lloyd et al. 2019⁶⁷ and applied it to the type 2 and 3. For consistency, the EAG applied patient utilities from HST24¹⁶ across the presymptomatic, type 1, and type 2 and 3 models. Our concerns around negative utilities from the presymptomatic model still applied here. The EAG also explored a scenario using patient utilities from SUNFISH.⁵³

The Roche model added separately the impact and costs of bulbar dysfunction, severe scoliosis, and non-permanent respiratory support on risdiplam and BSC using estimates from an internal, unpublished, natural history study. The EAG was concerned about the appropriateness of this approach given the risk of double-counting the impact of disease-related events, and the gap in the evidence regarding the impact of disease-modifying therapies in this area, therefore these were excluded from the base-case analysis. The EAG explored the impact of bulbar dysfunction in as a scenario to highlight the importance patients put on the impact of bulbar dysfunction.

The approach to incorporate carer utilities was the same for presymptomatic, type 1, and type 2/3 patients, therefore our concerns still applied here. The approach to include disease-related health care costs in type 2/3 model were sourced from an expert elicitation exercise conducted by Roche. For consistency in our approach, the EAG used health care costs from HST24¹⁶ but noted the large differences in disease-related costs in both approaches, and the lack of data in this area.

Cost-effectiveness results from Roche showed that including carer and patient HRQoL risdiplam compared to BSC showed that risdiplam was [REDACTED]. Results were sensitive to carer utilities at “sitting without support” and “not sitting”, the cost of risdiplam, and risdiplam treatment benefits at “sitting without support”.

The EAG analysis incorporated updated costs and mortality estimates to the most recent data, assumed a 10% increase in patient utility from treatment, and focused on patient HRQoL and ensuring alignment with the criteria for the severity modifier. The EAG also changed the time horizon from [REDACTED] in the Roche base-case to 90 years, although this was not expected to significantly alter the results. Our base-case analysis focused on risdiplam and BSC, with scenario analyses comparing risdiplam and nusinersen, using published evidence from Ribero et al. 2022.⁶⁴

The EAG's base-case analysis for risdiplam compared to BSC showed [REDACTED]. Results were sensitive to the drug cost of risdiplam, disease-related costs at “not sitting” for adults, utilities for “sitting without support”, and disease-related costs at “sitting without support” for adults. Using utility values from the Roche base-case or the SUNFISH trial, including carer utilities and changing the costs to the Roche base-case had a large impact on results [REDACTED]. The scenario comparing risdiplam to nusinersen showed that risdiplam was more effective and less costly than nusinersen, [REDACTED].

Overall, our conclusions on cost-effectiveness of nusinersen and risdiplam are broadly consistent with those reported by Biogen³¹ and Roche⁴⁴, and other HTA bodies such as CADTH (Canada)^{253,244} and ICER (US),⁷⁵ despite the differences in the model assumptions and input parameters.

However, these results are largely based on limited evidence and should be interpreted with caution. In the absence of robust comparative data, there remains insufficient evidence to reliably estimate the relative net health benefits of risdiplam, nusinersen or OA in patients with SMA. Therefore, there is a clear and continued need for further evidence to minimise the uncertainty in the cost-effectiveness analysis of these treatments for SMA.

16.2 Strengths and limitations of the assessment

16.2.1 Strengths

The EAG conducted a comprehensive assessment of the company submissions. These submissions were reviewed and critiqued in terms of the clinical evidence and economic models used to assess the effectiveness and cost-effectiveness of nusinersen and risdiplam. The EAG adhered to established NICE methods and best practices in health technology assessments to ensure a fair critique and assessment. The EAG conducted a thorough update of the previously conducted systematic review of the available literature assessing nusinersen and risdiplam, using standard systematic review methods.

Furthermore, the EAG also actively engaged with the clinical experts, and patient and professional organisations, to ensure the assessment accurately reflected the clinical practice and where possible, patients' voices were heard. The inclusion of the qualitative framework analysis meant that the clinical- and cost-effectiveness results were contextualised by the experiences of people with SMA, their families and caregivers. This included their experiences of both nusinersen and risdiplam treatment, highlighting individuals' perspectives on the treatments and what effects they may have had on their condition. The EAG conducted the framework analysis according to principles of CLIP-Q,⁷⁶ while coding and narratives surrounding the qualitative data were checked by independent researchers to ensure the analysis was adequately contextualised and no major subthemes were erroneously missed.

16.2.2 Limitations

The analysis was constrained by the lack of robust comparative data between treatments. The economic assessment had to rely on assumptions in the absence of long-term effectiveness data and discontinuations from treatment. Health state utility values incorporated into the model had significant impact on the cost-effectiveness of the treatments, however these values relied on previously collected data, mostly not representative of the trial population receiving these treatments. Moreover, results were often sensitive to the estimates of disease-related resource use, yet there was a lot of variation and uncertainty around these estimates.

In updating the clinical effectiveness SLR the EAG were unable to fully integrate the findings of the update with those of the previous SLR. In particular, the incorporation of additional outcomes identified as important by patients and professional groups was limited to the newly identified studies, in which reported data were limited for these outcomes.

The qualitative analysis was limited by several factors; these have been described in depth in Section 10.6. In brief, these limitations included: conducting a framework analysis instead of a thematic analysis; a lack of demographic information about the people included; some lack of clarity surrounding what treatment those included in the analyses were undertaking; the primary caregiver not being the respondent on behalf of children in the paediatric registry free-text data. These factors made it challenging to fully contextualise the qualitative data and, occasionally, to provide specific information surrounding peoples' experiences of nusinersen and risdiplam. It also limited the extent to which these data could be fully integrated with the other elements of the appraisal.

17 Conclusions

The previously completed technology assessments highlighted a lack of longitudinal and comparative data for nusinersen (TA588) and risdiplam (TA755). This has been addressed by longer follow-up periods of the clinical trials (~8 years for nusinersen and 5 years for risdiplam) and the use of an MAA to provide further data. For both nusinersen and risdiplam, there is evidence of maintenance or improvement of motor functions. Maintenance should be considered extremely beneficial in this patient population, as emphasised by both patients and professionals. Both drugs had an impact on mortality: for type 1 patients, compared to natural history median of 10 months life expectancy, 75% of patients were still alive on nusinersen after three years and 91% of patients on risdiplam after five years. There were no deaths in the presymptomatic group in any of the included studies. Patients with types 2 and 3 have substantially greater life expectancy and an impact of treatment would likely require much longer follow-up to be evidenced. Other evidence, such as quality of life and other patient reported outcomes, show mixed results for both nusinersen and risdiplam. There is a lack of direct comparative evidence between the two treatments and the available gene therapy. The original technology assessment for risdiplam noted that there was a lack of comparative evidence to usual care for type 1 patients. There is still no clinical trial comparing type 1 patients receiving risdiplam to treatment-naïve patients. However, the differences in eligible populations for each of the treatments means direct comparisons are difficult. There is also a lack of data for some outcomes deemed important by patients, carers, and professionals, such as bulbar function and stamina and fatigue, which conclusions difficult to make.

The cost-effectiveness studies included in the original SLR and the SLR update varied based on the target population considered, interventions and comparators included, outcomes, modelling methods, resource use and costs, health-state utility estimates, time horizons, analyses, assumptions and limitations, and patient and professional groups engagements. There was a consensus about the type of models adopted for SMA cost-effectiveness evaluation being Markov models. But the results of the SLR indicate a need for robust and reliable data on treatment effectiveness, real-world evidence generation of utility estimates and consensus in adopting resource use and estimating costs for SMA treatment evaluation.

Cost-effectiveness results by the EAG for the presymptomatic population suggested that both risdiplam and nusinersen have the potential to be [REDACTED] compared against BSC without a disease-modifying therapy, caveating that the evidence base in this area is still weak and relies on single-arm studies. Due to gaps in the evidence, it was challenging to compare across DMTs.

Cost-effectiveness results by the EAG for the type 1 population showed that both risdiplam and nusinersen were [REDACTED] when compared against BSC without a disease-modifying therapy. Further analysis showed that across both drugs it was plausible that they would not be considered cost-effective against no treatment even assuming zero drug costs. This counter-intuitive result arises from the high health-care resource use associated with patients whose mobility is below the level of being able to stand- exceeding what the health-care system is typically willing to pay. However, meaningful comparison across disease modifying therapies remains challenging because of significant evidence gaps.

Cost-effectiveness results by the EAG for the type 2 and 3 population showed that both risdiplam and nusinersen were [REDACTED] interventions when compared against BSC without a disease-modifying therapy. Relative to the more severe disease types above in this

patient population the benefits of both drugs were less clear-cut, with therapies helping patients maintain the motor milestones gained.

The cost-effectiveness results are largely based on limited evidence and should be interpreted with caution. In the absence of comparative data, the EAG concludes that there is insufficient evidence to estimate the relative net health benefits of comparing risdiplam to nusinersen for patients with SMA. Therefore, there is a clear and continued need for further evidence to minimise the uncertainty in the cost-effectiveness analysis of these treatments for SMA.

17.1 Suggested research priorities

There is a lack of evidence comparing nusinersen to risdiplam and either or both treatments to OA. While the eligibility criteria means there are currently differences in the populations being treated by the respective treatments, future research could aim to conduct a randomised controlled trial for DMTs. Additionally, trials assessing the safety, efficacy and cost-effectiveness of combined treatments (i.e. nusinersen, risdiplam, and OA) would provide evidence of any incremental benefits that may be available.

Risdiplam still requires evidence for type 1 patients compared to a control (usual care) group. The clinical trial for type 1 (FIREFISH) is a single arm trial. Risdiplam should therefore be assessed in a comparative clinical trial for type 1 SMA patients.

A consistent issue highlighted throughout the review process, especially within the qualitative data, is the lack of sensitivity of motor function assessment tools. There is a focus on gross motor skills, such as sitting, rather than fine motor skills (e.g. wheelchair control) that are likely to be important for quality of life; indeed, these were highlighted in the qualitative analyses as being important functions. Further work should look to ascertain what changes in motor function are important to patients, carers, and professionals and ultimately to incorporate these into future assessments.

While the MAA has generated some real-world data, alongside other observational studies identified in the literature, there is still a lack of long-term evidence for some outcomes. For example, HRQoL and other PROMs are generally lacking. It will be important to continue to capture such outcomes, as there is currently a sparsity of data, and this leads to uncertainty about the impact of treatments. Future research should look to further capture important QoL measures over an extended period.

The cost-effectiveness results for the presymptomatic population showed the sooner patients are treated the better value for money disease-modifying therapies represent, which leads to questions around the value of testing to maximise the value of these therapies. The economic analysis for the symptomatic populations with types 1, 2 and 3 further showed the importance of exploring the disease-related resource use for the NHS and for carers and similarly the disease-related quality of life for patients and carers.

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19 Appendices

19.1 Appendix 1: Search critique and MEDLINE strategy for EAG systematic review

The previous review conducted combined clinical effectiveness and economic website searches on 25/01/24, the main clinical effectiveness database searches on 29/01/24, The main economic database searches on 30/01/24 and 31/01/24. The previous review reports the use of economic design filters. Conference abstracts were sought on all databases as part of the search. The previous review states that date and language limitations were imposed on the searches, dates aligning with the last company submissions for single technology appraisal. A summary of the search-related information is provided in the table below.

The search strategy encompassed concepts from the population, combined with the intervention, and date limitation concepts of the decision problem.

The EAG appraised the searches using the PRESS checklist and the latest NICE methods manual⁴⁰. The number of records retrieved per search line was shown and the methods and terms used to search the conference abstracts were presented as might be expected when using the PRISMA-S reporting guidance.

EAG comments:

- All relevant studies were attained by the searches.
- Multidisciplinary electronic databases were searched and described in full, including platform, date of search, search terms, retrieved numbers, and date of coverage.
- Relevant search terms were used and combined appropriately. However, we query the use of [(spinal muscul* atroph* or SMA)] search terms, and whether this should have been an adjacency search to ensure coverage of spinal and bulbar muscular atrophy and spinal progressive muscular atrophy.
- Search terms were based on a search strategy from a previous Cochrane review. This was reported but no justification was given for adaption of the search strategy (for example the removal of terms that did not meet the population outlined in the decision problem). An economic study design filter was used and appropriately referenced/reported. No alterations were made to the filter.
- Searches excluded animal study terms, as standard practice.
- Date limitations were applied with justification. However, justification for English language limitations was not given.
- No individual conferences were searched; however, conference abstracts were included in the search strategy.
- Clinical trial databases were searched for ongoing/unpublished trials.

Search strategies	Details
Clinical effectiveness database searches	29/01/24 Data limitations specific to interventions

Search strategies	Details
	Nusinersen – 01/01/2017 onwards Risdiplam – 01/01/2020 onwards Limited to English language
Economic database searches	30/01/24 or 31/01/24 Data limitations specific to interventions Nusinersen – 01/01/2017 onwards Risdiplam – 01/01/2020 onwards Limited to English language
Combined clinical effectiveness and economic website searches	25/01/24 Limitations applied where feasible Data limitations specific to interventions Nusinersen – 01/01/2017 onwards Risdiplam – 01/01/2020 onwards Limited to English language

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to March 10, 2025

#	Searches	Results
1	exp Muscular Atrophy, Spinal/	7026
2	(spinal muscul* atroph* or SMA).mp.	36085
3	(Werdnig adj Hoffman*).mp.	404
4	(Kugelberg adj Welander*).mp.	214
5	1 or 2 or 3 or 4	37966
6	(Nusinersen or spinraza* or isis smn* or isis 396443).mp.	961
7	(Risdiplam or evrysdi* or RG 7916 or RG7916).mp.	258
8	5 and 6	913
9	5 and 7	238
10	(201710* or 201711* or 201712* or 2018* or 2019* or 2020* or 2021* or 2022* or 2023* or 2024* or 2025*).dt,ez,da,cb.	11727236
11	8 and 10	902
12	limit 8 to yr="2017 -Current"	905
13	11 or 12	907
14	(2020* or 2021* or 2022* or 2023* or 2024* or 2025*).dt,ez,da,cb.	8802194
15	9 and 14	230
16	limit 9 to yr="2020 -Current"	230
17	15 or 16	230
18	(exp Animals/ or exp Animal Experimentation/) not (Humans/ or exp Human Experimentation/)	5315416

#	Searches	Results
19	Editorial.pt.	722508
20	13 or 17	972
21	20 not (18 or 19)	933
22	limit 21 to english language	894

19.2 Appendix 2: Domains and sub-domains included in the data extraction spreadsheet for each drug

Admin

- Reviewer
- Checker

Study characteristics

- First author surname
- Year
- Trial name
- Title
- Publication type
- Linked records
- Primary reference? (yes/no)
- NCT number
- Countries
- Funding sources
- COIs
- Design
- Aims
- Setting / data source
- Inclusion criteria
- Exclusion criteria

Intervention details

- Treatment name
- Method of administration
- Dose
- Frequency
- Treatment duration
- Switch between treatments?(yes/no with details)
- Treatment fidelity

Intervention group patient characteristics

- SMA sub-type
- Number of SMN2 copies
- Age
- Sex
- Comorbidities
- Prior treatments
- Sample size (enrolled)
- Sample size (analysed)
- N and reasons for withdrawal

Comparator group 1 (for between group studies)

- Treatment name
- Method of administration
- Dose
- Frequency
- Treatment duration
- Switch between treatments? (yes/no with details)

Comparator group 1 (for between group studies) patient characteristics

- SMA sub-type
- Number of SMN2 copies
- Age
- Sex
- Comorbidities
- Prior treatments
- Sample size (enrolled)
- Sample size (analysed)
- N and reasons for withdrawal

Data analysis

- Statistical method
- Sub-group analyses

Conclusions

- Author conclusions
- Reviewer conclusions

Admin

- Reviewer
- Checker

Reference

- First author surname
- Year
- Title

Motor function

- Measurement tool
- Follow-up time
- Results

Adverse effects of treatment

- Measurement tool
- Follow-up time
- Results

Bulbar function

- Measurement tool
- Follow-up time
- Results

Hospitalisation

- Measurement tool
- Follow-up time
- Results

Respiratory function

- Measurement tool
- Follow-up time
- Results

Complications of SMA

- Measurement tool
- Follow-up time
- Results

Need for ventilation

- Measurement tool
- Follow-up time
- Results

Stamina and fatigue

- Measurement tool
- Follow-up time
- Results

Mortality

- Measurement tool
- Follow-up time
- Results

Health-related quality of life (patients and carers)

- Measurement tool
- Follow-up time
- Results

ADLs

- Measurement tool
- Follow-up time
- Results

Ability to socialise

- Measurement tool
- Follow-up time
- Results

Emotional impact

- Measurement tool
- Follow-up time
- Results

Independence

- Measurement tool
- Follow-up time
- Results

Impact on education

- Measurement tool
- Follow-up time
- Results

Impact on ability to work

- Measurement tool
- Follow-up time
- Results

Impact on family and carers

- Measurement tool
- Follow-up time
- Results

Looking to the future (e.g., anticipatory grief, hope for the future)

- Measurement tool
- Follow-up time
- Results

Maintenance and stabilisation of condition

- Measurement tool
- Follow-up time
- Results

Patient choice

- Measurement tool
- Follow-up time
- Results

Spectrum of SMA

- Measurement tool
- Follow-up time
- Results

19.3 Appendix 3: Data extraction sheet (economic evaluation review)

Table 130: Completed data extraction sheet of an economic analysis in the economic evaluation systematic review update

Study details

Study title	Onasemnogene Apeparvovec Gene Therapy and Risdiplam for the Treatment of Spinal Muscular Atrophy in Thailand: A Cost-Utility Analysis
First author	Khuntha
Co-authors	Prawjaeng, J., Ponragdee, K., Sanmaneechai, O., Srinonprasert, and Leelahavarong, P.
Source of publication Journal yy;vol(issue):pp	Applied Health Economics and Health Policy 2025;23:277-290
Publication link	https://doi.org/10.1007/s40258-024-00915-y
Language	English
Publication type	Journal article
Inclusion criteria/study eligibility/PICOS	
Population	Patients with symptomatic SMA patients (SMA type 1 age onset at 3 months, SMA type 2 age onset at 12 months, and SMA type 3 age onset at 18 months)
Intervention(s)	•Patients with SMA type 1: risdiplam plus diagnosis and SOC, or onasemnogene abeparvovec plus diagnosis and SOC •Patients with SMA type 2-3: risdiplam plus diagnosis and SOC
Comparator(s)	Disease diagnosis and SOC
Outcome(s)	Life-years (LYs), and quality-adjusted life-years (QALYs)
Study design	Economic Evaluation (cost-utility analyses)
Methods	
Target population and subgroups	SMA type 1 age onset at 3 months, SMA type 2 age onset at 12 months, and SMA type 3 age onset at 18 months, based on disease severity and treatment indications
Setting and location	Thailand
Approach to engagement with patients and others affected by the study	Interviews with patients and caregivers provided data on non-medical costs and utilities.

Study perspective	Thai health care system
Comparators	Standard of care (comprehensive approach encompassing various domains: (1) rehabilitation and bone management; (2) nutrition and swallowing care; (3) respiratory care; (4) care for other bodily systems; (5) ethical and palliative care; (6) attention to educational, emotional, and socioeconomic aspects; (7) utilization of traditional medicines; and (8) the facilitation of assistive devices essential for the patient's daily activities)
Time horizon	Time horizon: •SMA types 1-3: Lifetime horizon Cycle length: •Under the SOC, patients may experience a deteriorating health state or remain stable, while in the onasemnogene and risdiplam group, patient outcomes may improve or worsen depending on the treatment responses. These transitions occur within a 6-month cycle length according to the natural history of the disease as defined in the CHOP INTEND outcome measure.
Discount rate	3% annual discount rate
Outcome(s)	Life-years (LYs), and quality-adjusted life-years (QALYs)
Measurement of effectiveness	The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorder (CHOP INTEND)
Measurement and valuation of preference-based outcomes	The EQ-5D-Y questionnaire (a youth version of the EuroQol measure) translated into Thai was used to interview patients and caregivers. In the absence of an EQ-5D-Y valuation study for Thailand, the published tariff from Japan (Shiroiwa et al., 2021; doi:10.1177/0272989X211001859), viewed as a prototypical country in Asia, was obtained to calculate utility values. Because of the limited number of patients, only the (A) BRND, (C) sitting, and (E) PAV health states were observed. Consequently, values for the other health states were deduced using a percentage of the difference between each health state from a study in China (Hu et al., 2022; doi.org/10.3389/fpubh.2022.1054931) that collected utility values for SMA patients from the Chinese EQ-5D-Y using data from the Chinese EQ-5D-3L valuation study as a proxy.
Methods for identifying resource use	•Hospital data bases and pharmaceutical companies •Patient and caregiver interviews
Resource use and costs	•Direct medical costs for the current practice include disease diagnosis, assistive equipment such as wheelchairs, ventilator and maintenance costs, body support, and medication costs during ambulatory care and hospitalization. •Direct non-medical costs including accommodation, transportation, meals, and indirect costs including other out-of-pocket charges for informal care, and productivity costs from caregivers.

Data source of resource use	•The costs of medical devices or equipment were retrieved from the hospital. Likewise, charges for the 114 SMA patients incurred from both out- and in-patient care were collected from the hospital database between January 2016 and December 2021, and these charges were adjusted to costs using the hospital-based ratio of charge-to-cost. The costs were calculated for each health state in each SMA subtype. •For the costs of the new treatments, pharmaceutical companies submitted drug prices for assessment in this study only. •Direct non-medical costs and productivity costs from caregivers were collected from patient and caregiver interviews during hospital visits. The interview was conducted between June 2022 and February 2023; of 114 cases, patients from 3 cases for SMA type 1 and 12 cases for SMA types 2–3 had hospital visits and were able to interview
Currency, price date and conversion	All costs were adjusted to 2023 values using the consumer price index (CPI) and the recommended WTP threshold of 4444 US dollars (USD) per QALY gained (i.e., 160,000 Thai baht per QALY gained using an exchange rate of 1 USD ≈ 36 THB)
Analytic approach and model type (if applicable)	Model: •A Markov model was constructed to simulate the progression of disease on the basis of the CHOP INTEND outcome measure. The model's population consisted of symptomatic SMA patients categorized into two groups: SMA type 1 age onset at 3 months, SMA type 2 age onset at 12 months, and SMA type 3 age onset at 18 months, based on disease severity and treatment indications. The SMA type 1 group received either onasemnogene or risdiplam, where the comparative choices included (i) onasemnogene plus diagnosis and SOC and (ii) risdiplam plus diagnosis and SOC, compared with (iii) disease diagnosis and SOC alone. The SMA types 2–3 group received risdiplam, where the comparative options included (i) risdiplam plus diagnosis and SOC and (ii) disease diagnosis and SOC alone. These decision-analytic alternatives are mutually exclusive, where the probability of each option is separate, resulting in the adoption of one of the interventions. Drug administrations for SMA type 1 and 2–3 were based on their age and weight. States: (A) a broad range of normal development (BRND; defined as able to walk independently); (B) walking with support or equivalent to SMA type 3; (C) sitting (defined as able to sit without support, stand alone, or stand with assistance) or equivalent to SMA type 2; (D) not sitting but living ventilation-free (defined as lacking head control, voluntary grasping, voluntary kicking or rolling over completely, and not requiring permanent ventilation) or equivalent to SMA type 1; (E) permanent assisted ventilation (PAV; defined as 16 or more hours per day of breathing support) or equivalent to SMA type 1; and 'Death'. Other points: •The Assessment of the Validation Status of Health-Economic decision models (AdViSHE) tool was used to evaluate four aspects of

	validation: (1) validation of the conceptual model; (2) input data validation; (3) validation of the computerized model; and (4) operational validation Transitional probabilities •Under the SOC, the 6-month transitional probabilities were analysed for SMA patients at one of the largest Faculties of Medicine in Bangkok, Thailand, from the first diagnosis in 1999 to the current diagnosis in 2021, which included 114 patients. •Onasemnogene effectiveness, derived from clinical trials [NCT02122952, NCT03306277, NCT03461289] and unpublished data, was provided by the pharmaceutical company to calculate health state transitions. Two probabilities were observed from the data, namely (D) not sitting to (C) sitting and (C) sitting to (B) walking transitions. •Deaths, as reported from the clinical trials [NCT02122952, NCT03306277, NCT03461289], were compared with the SOC in Thailand. •For risdiplam, unpublished data from clinical trials were provided by the pharmaceutical company for the calculation of health state transitions and mortality for both SMA type 1 [NCT03306277, NCT03461289] and types 2–3 [NCT02391831, NCT02908685].
Assumptions	•Patients entering the model were confirmed SMA by genetic testing. The population in this study was confirmed to be SMA as symptomatic patients who passed genetic testing. So, the related costs were included. •Patients entering the model can start at any health state by adjusting the proportion from data of Thai patients. Once patients are diagnosed, they have different disease severity according to the age of onset and the number of SMN2 copies. So, patients can start in the model at any health state to be consistent with the nature of the disease. •Patients have a chance to move to any health state. In this study, a 6-month cycle length was used. So, patients can improve or worsen their health states according to clinical evidence and the experts •The effect of onasemnogene was assumed to prolong the lifetime of patients despite it being administered once. According to the indication of onasemnogene, it is administered once in the early stage of a patient's life. Moreover, it is a gene replacement that would yield a normal gene once it is fixed. Although the follow-up periods after treatment in the clinical studies were not long enough to capture a lifetime, the effects will be extrapolated based on the longest follow-up time (i.e., 12-24 months). •The mortality rate from other causes of death will be applied to death in the general population in Thailand. In this model, all patients have a chance of death from other causes in addition to disease-related mortality. So, the life table of death in the general population will be used to inform this value.
Results	
Study parameters	Characteristics of patients included in the study, transitional probability in the SOC, mortality rate in the SOC, probability of death in the general population in Thailand, treatment effects of onasemnogene and risdiplam, drug administration and unit costs of onasemnogene and risdiplam, risdiplam price per age and body

	weight in the Thai population, direct medical costs in the current practice, direct non-medical and indirect costs, disutility
Total QALYs	SMA type 1: •Onasemnogene: 11.66 •Risdiplam: 6.56 •SOC: 1.82 SMA type 2-3: •Risdiplam: 15.83 •SOC: 10.71
Total LYs	SMA type 1: •Onasemnogene:16.09 •Risdiplam: 12.51 •SOC: 3.07 SMA type 2-3: •Risdiplam: 22.01 •SOC: 16.00
Total Costs	SMA type 1: •Onasemnogene: 1900000 •Risdiplam: 1045000 •SOC: 294000 SMA type 2-3: •Risdiplam: 2753000 •SOC: 211000
ICER/QALY:	USD/QALY gained: •SMA type 1: Onasemnogene vs SOC: 163102 •SMA type 1: Risdiplam vs SOC: 158357 •SMA type 2-3: Risdiplam vs SOC: 496704
Characterising uncertainty	•Sensitivity analysis was used to examine the effects of uncertainties on the model's input parameters. One-way sensitivity analysis (OWSA) was used to assess each parameter's impact on the ICER by varying its lower bound and upper bound values while holding all other parameters constant. •Probabilistic sensitivity analysis was used to assess the uncertainties of all parameters at once using a Monte Carlo simulation with 1000 iterations •Scenario analysis was used to calculate ICER values at different percentages of reduction in treatment costs
Discussion	
Study findings	•For SMA type 1, given a WTP threshold of 4444 USD per QALY gained, the SOC has a 99% chance of being cost effective. If the WTP threshold were increased to 153,000 USD per QALY gained, both onasemnogene and the SOC would share similar probabilities (36%). If the WTP were to reach 278,000 USD per QALY gained, onasemnogene would have a 76% chance of being cost-effective. •For SMA types 2–3, given the current WTP threshold, the SOC is the 100% cost-effective option. Risdiplam and the SOC would have similar probabilities of being cost-effective (i.e., 54% versus 46%)

	were the WTP threshold to approach 500,000 USD per QALY gained. Likewise, risdiplam would have a 99% chance of being a favourable treatment were the WTP value to soar past 556,000 USD per QALY gained
Limitations	•Adverse events from treatments were excluded because of the nature of the disease and its numerous complications, although the costs and ebbing quality of life resulting from adverse events were implicitly included in medication costs and utilities per each health state. •While this study optimized the benefits of using real-world data from Thai patients to calculate transitional probabilities in the SOC, rather than data using derived from clinical trials, only rare cases were available, thus the data could only be analysed for the transition from health states (D) not sitting to (E) PAV in SMA type 1. •Because the clinical trials encountered a limited number of patients, with rare cases and characteristics, there was concern over the applicability of the effectiveness data. The clinical trials were single-arm, open-label, nonrandomized, and non-blinded, with a historical cohort as a control. Due to a limited number of treatment options for a well-characterized and life-threatening disease, conducting a placebo-controlled study was considered unethical, making it one of the few data sets available for this study •In addition, the patient data in this study relied on a single site, albeit one that represented 50% of all patients in the country, the consideration of this finding for the national policy should be made cautiously. Given the rare cases, only the (D) not sitting to (E) PAV health state transition could be analysed for SMA type 1. Besides that, the mortality data for SMA types 1 and 2–3 were aggregated because there was inadequate data to analyse each health state on its own. Some medical costs in SMA type 1 were also borrowed from SMA types 2–3, in the case of health states (A) BRND, (B) walking, and (C) sitting. •For the utility values, 15 cases represented only health states (C) sitting and (E) PAV. Hence, a study from a similar setting in China was obtained to inform any proportional adjustments to the other health states.
Generalisability	See limitations above.
Other	
Source of funding	Open access funding provided by Mahidol University. This study was supported by the Siriraj Research Developmental Fund, Faculty of Medicine Siriraj Hospital, Mahidol University [grant no. (IO) R016532007]
Conflicts of interest	The authors declare that they have no conflicts of interest

Comments	Even though risdiplam and onasemnogene are available in Thailand, these treatments are not yet included on the reimbursement list for the Thai universal health coverage (UHC) plan. In early 2023, the Rare Disease Care Working Group under the National Health Security Office (NHSO) Subcommittee for Scopes and Types of Health Services, which oversees the Thai UHC reimbursement list, together with the Subcommittee for the National List of Essential Medicines (NLEM), which administers the Thai pharmaceutical reimbursement list, required supporting evidence before determining whether the novel therapies should be included in the reimbursement lists. Therefore, this study aimed to evaluate the cost-utility of the existing Thai FDA-approved treatments (namely risdiplam and onasemnogene) in addition to the current healthcare services for SMA including disease diagnosis and SOC.
Authors conclusion	While onasemnogene and risdiplam exceeded the value-for-money threshold of the Thai healthcare system, they yielded the highest QALY gains among all approved medications. Policymakers should incorporate various pieces of evidence alongside the cost-effectiveness results for rare diseases with costly drugs. Additionally, cost-effectiveness findings are useful for price negotiations and alternative financial funding, which allows policymakers to seek solutions to ensure patient access, aligning with universal health coverage principles in Thailand.
Reviewer's conclusion	From a Thai context neither onasemnogene nor risdiplam were shown to be cost-effective for SMA type 1. In addition, risdiplam was not cost-effectiveness for SMA types 2-3. Discount rates for both costs and outcomes were the most influential parameters to the calculated mean ICER values. In a scenario analysis, despite drug price reductions of up to 75% neither treatment option achieved cost-effectiveness in the Thai context. Although there were limitations within this study, it is reported to be one of the first studies to investigate the cost-utility of onasemnogene and risdiplam in symptomatic SMA types 1, 2, and 3 patients in the LMIC context. While highlighting the ICERs of these treatments are high, this study provides evidence on the economic and health consequences of these high-cost treatments for policy consideration in other LMIC settings.

19.4 Appendix 4: Table of included studies for nusinersen

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
AlRuthia 2021 ¹⁶¹	Saudi Arabia	Parents/ carers interviewed	Cross sectional	n = 36 parents/carers Patients: Nusinersen: Type 1 (54%), other types NR	Standard care: Type 1 (25%), type 2 (53%), type 3 (22%)	HRQoL	NA	NR
AlTawari 2024 ²⁶³	Kuwait	Treatment centres	Retrospective Case series	n = 38 Paediatric: n = 20 Type 1 (40%), type 2 (40%), type 3 (20%) Adult: n = 18 Type 2 (11%), type 3 (89%)	NA	Motor function Adverse effects	NA	80 months
Aragon-Gawinska 2020 ¹²⁹	France, Belgium	Registry data	Retrospective Before after	n = 53 Type 1 Mean age = 22 months	NA	Motor function Mortality Adverse effects	Sitter, non-sitter	14 months
Arsilan 2023 ²¹⁷	Turkey	Treatment centre	Prospective Before after	n = 32 Type 2 (19%), type 3 sitters (50%), type 3 walkers (31%) Median age = 33.5 years	NA	Motor function Adverse effects ADL	NA	23 months
Audic 2020 ¹⁸³	France	Treatment centres	Retrospective Before after	n = 123 Type 1 (28%), type 2 (72%)	NA	Motor function Nutrition support Ventilation Adverse effects	<2 years, >2 years	1 year
Audic 2024 ¹⁸⁰	France	Treatment centres	Retrospective Before after	n = 57 Type 1 (56%) , type 2 (44%) Median age = 16 months	NA	Motor Nutrition support Ventilation Complication Socialisation	NA	36 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
Axente 2022 ¹⁸⁸	Romania	Treatment centre	Retrospective Before after	n = 34 Type 1 (32%), type 2 (47%), type 3 (21%)	NA	Motor function	NA	26 months
Bahadir Senol 2025 ⁹⁸	Turkey	Hospital files	Retrospective Before after	n = 33 Type 1 (45%), type 2 (41%), type 3 (12%)	NA	Motor function Adverse effects	NA	NR
Barp 2023 ⁹⁹	Italy	Treatment centre	Prospective controlled	n = 37 Nusinersen: n = 17 Type 2 (57%), type 3 (43%) Healthy control: n = 20	Healthy controls	Motor function	NA	NR
Belancic 2023 ¹⁹²	Croatia	Treatment centres	Retrospective	n = 52 Type 1 (35%), type 2 (12%), type 3 (54%) Median age = 13.4 years	NA	Motor function Feeding support Respiratory function Treatment switch	NA	NR
Berti 2022 ¹³⁰	Italy	Treatment centre	Prospective Before after	n = 20 Type 1 Mean age = 6.5 months	NA	Oral and swallowing	Normal swallowing Tube feeding + by mouth Tube feeding no tracheostomy Tracheostomy + tube feeding	62 months
Bjelica 2023 ²²⁶	Germany	Treatment centre	Prospective Before after	n = 38 Type 1 (3%), type 2 (37%), type 3 (55%), type 4 (5%) Mean age = 38.4 years	NA	Motor function Respiratory function Fatigue QoL	SMA types SMN2 copy number Baseline HFMSE score Previous spinal infusion	30 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
							Use of NIV Use of PEG	
Bonanno 2020 (child) ¹⁰⁰	Italy	Treatment centre	Prospective Before after	n = 21 Type 2 (76%), type 3 (24%)	NA	Motor function	NA	6 months
Bonanno 2022 (adult) ¹⁰¹	Italy	Multiple treatment centres	Retrospective Before after	n = 78 Type 2 (9%), type 3 (88%), type 4 (3%)	NA	Motor function Fatigue HRQoL	Sex SMN2 copies Disease duration	14 months
Brakemeier 2021 ²¹⁴	Germany	Treatment centre	Prospective Before after	n = 57 Type 2 (55%), type 3 (45%) Mean age = 38.5 years	NA	Motor function Bulbar function	SMA type	14 months
Cavaloiu 2024a ²⁶⁴	Romania	Treatment centres	Prospective Before after	n = 37 Type 2 (62%), type 3 (38%) Median age = 29 years	NA	Motor function	NA	54 months
Cavaloiu 2024b ²⁶⁵	Romania	Treatment centres	Prospective	n = 43 Type 1 (12%), type 2 (60%), type 3 (28%) Median age = 20 years	NA	HRQoL	NA	6 months
Chacko 2022 ¹⁹³	Australia	Treatment centre	Prospective Before after	n = 28 Type 1 (25%), type 2 (43%), type 3 (32%)	NA	Motor function	NA	12 months
Chen 2024 ²⁶⁶	China	Treatment centre	Retrospective Before after	n = 52 Type 1 (10%), type 2 (77%), type 3 (13%) Median age = 44.5 months	NA	Motor function	NA	14 months
CHERISH ²⁸	International	Treatment centres	Prospective RCT	Nusinersen: n = 84 Type 2 and 3 Sham: n = 42 Type 2 and 3	Sham injection	Motor function	NA	15 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
Chiriboga 2016 ¹⁶⁴	USA	Treatment centres	Prospective Before after	NR	Nusinersen at different doses	Safety Tolerability Motor function Quality of life	NA	9-14 months
Cho 2023 ¹⁹⁹	South Korea	Dataset 1: Reimbursement data Dataset 2: Treatment centres	Retrospective Before after	n = 137 Type 1 (15%), type 2 (75%), type 3 (9%)	NA	Motor function	NA	1, 2 and 3 years
Coratti 2021 ¹⁴¹	Italy, USA, UK	Specialised neuromuscular sites	Prospective Before after	n = 77 Type 2 Mean age = 7.47 years	NA	Motor function	Age	12 months
Coratti 2024 ¹⁴⁰	Italy	iSMAC consortium	Retrospective Before after	n = 130 Type 2	NA	Motor function	Age	12 months
CS2/CS12 ²¹⁹	USA	Treatment centres	Prospective	n = 47 Type 2 (39%), type 3 (61%) Mean age = 8 years	NA	Motor function Adverse effects	NA	6 months post-treatment
D'Amico 2019 ¹⁰²	Italy	EAP (Italy), 1 hospital	Prospective Before after	n = 57 Type 1 (66%), types 2 and 3 (33%)	NA	Motor function Bulbar function Respiratory function Adverse events QoL	NA	NR
de la Banda 2021 ¹⁶⁵	France	Treatment centres	Prospective Before after	n = 54 Type 1 and 2 Mean age = 8.2 years	Untreated controls	Motor function	NA	6 months
De Wel 2021 ²⁰⁸	Belgium	Treatment centre	Prospective/ Retrospective	n = 64 Types 3 and 4 Mean age = 6.5 years	NA	Motor function	NA	14 months
Duan 2022 ¹²¹	China	Beijing Meier Advocacy & Support Center for SMA (Meier)	Prospective Non-randomised trial	Nusinersen: n = 51 Type 1 (27%), type 2 (59%), type 3 (14%) Non-medication: n = 281	Treatment naïve	HRQoL	NA	Three surveys conducted: December 2019, April 2020 and

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
				Type 1: (16%), type 2 (59%), type 3 (25%)				September 2020
Duong 2021 ²²²	USA	NR	Prospective Before after	n = 42 Type 2 (43%), type 3 (57%) Mean age = 34 years	NA	Motor function Respiratory function	SMA type SMN2 copies Functional status History of spinal surgery	24 months
EAP (multiple) ¹⁰⁹	International	EAP (multiple locations), Treatment centre	Prospective Cohort study	n = 33 Type 1 Median age = 21.3 months	NA	Motor function Respiratory function	SMN2 copies	6 months
Edel 2021 ¹²⁸	UK	EAP (UK)	Prospective Before after	n = 20 Type 1 Median age = 9.5 months	NA	Respiratory function	NA	18 months
EMBRACE ²⁹	US/Germany	Treatment centres	Prospective RCT	Nusinersen: n = 14 Multiple types, patients who are ineligible for ENDEAR and CHERISH Sham: n = 7 Multiple types, Multiple types, patients who are ineligible for ENDEAR and CHERISH	Sham injection	Adverse effects		14 months
ENDEAR ²⁷	International	Treatment centres	Prospective RCT	Nusinersen: n = 80 Type 1 Sham: n = 41 Type 1	Sham injection	Motor function Time to death or permanent ventilation Survival		13 months
Erdem 2024 ²¹³	Turkey	Treatment centre	Retrospective Before after	n = 31 Type 2 (6%), type 3	NA	Motor function QoL	NA	15 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
				(94%) Mean age = 36 years				
Fainmesser 2022 ²⁰²	Israel	Treatment centre	Prospective Before after	n = 37 Type 2 (41%), type 3 (59%) Mean age = 38 years	NA	Motor function Respiratory function	NA	Baseline, 6 months, then every 4 months up to 30 months
Finkel 2021 ¹³¹	USA/Canada	Treatment centres	Prospective Before after	n = 23 Type 1 Mean age = 141 days	NA	Motor function Event-free survival Adverse events	SMN2 copies	3.7 years
Freigang 2021a ²⁶⁷	Germany	Nine neurological specialist care centres	Retrospective Before after	n = 234 Type 2 (34%), type 3 (66%) Mean age = 36.2 years	NA	Motor outcomes	NA	18 months
Freigang 2021b ¹²⁶	Germany	4 motor neuron disease specialist centres	Prospective Controlled	Nusinersen: n = 79 Type 1, 2 and 3 Mean age = 31 years Healthy controls: n = 30	Controls matched by age and sex; not administered nusinersen	Motor	SMA type SMN2 copies	14 months
Freigang 2023 ²²⁵	Germany	Neurology department of one hospital	Prospective Before after	n = 24 Type 2 (42%), type 3 (58%)	NA	Respiratory function	NA	Follow-up visit 1: n=22, 15.5 months Follow-up visit 2: n=19, 26.6 months Follow-up visit 3: n=9, 38.3 months
Gaboli 2024 ²⁶⁸	Spain	EAP (Spain); Hospital	Prospective Before after	n = 28 Type 1 (39%), type 2 (43%), type 3 (19%)	NA	Bulbar function Respiratory function	NA	24 months
Gauthier 2021 ¹⁰⁴	USA	Dataverse claims database (US)	Retrospective Before after	Mean age and SD (median in brackets) Type 1 discontinuation (n=11): 0.82 ± 0.75	NA	Speech therapy Need for nutritional support - gastrostomy Nasogastric tube	Discontinuation versus no discontinuation Adherent	NR

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
				(1.00) Type 1 non-discontinuation (n=12): 0.67 ± 0.49 (1.00) Type 2 discontinuation (n=24): 2.92 ± 1.61 (3.00) Type 2 non-discontinuation (n=17): 2.76 ± 1.03 (3.00) Type 3 discontinuation (n=146): 12.49 ± 8.53 (10.00) Type 3 non-discontinuation (n=114): 17.53 ± 11.44 (14.50)			versus non-adherent	
Goedeker 2024¹⁴⁸	USA	Local tertiary care centres	Retrospective Before after	n = 29 Mean age at last follow-up: 8.5 months	NA	Adverse events ventilation motor functions mortality	NA	N/A - retrospective , reviewed laboratory reports
Gonski 2023¹⁷⁸	Australia	Two tertiary treatment sites	Retrospective Before after	n = 48 Type 1 (21%), type 2 (48%), type 3 (31%) Mean age = 6.98 years	NA	Motor function Hospitalisations Respiratory function Ventilation	NA	2 years before and 2 years after treatment started
Govoni 2024¹⁴²	Italy	Multiple treatment centres	Retrospective Before after	Type 3 Mean age = 39.7 years	NA	Motor function Fatiguability	NA	14 months
Gunther 2024²¹¹	Germany, Austria and Switzerland	SMArtCare platform	Prospective Before after	n = 237 Type 1: 14 months: 5/237 (2%), 26 months: 3/171 (2%), 38 months: 2/120 (2%) Type 2: 14 months:	NA	Motor function	NA	171 patients with a treatment period of 26 months, and 120 patients

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
				67/237 (28%), 26 months: 44/171 (26%), 38 months: 33/120 (27%) Type 3: 14 months: 156/237 (66%), 26 months: 117/171 (68%), 38 months: 83/120 (69%) Type 4: 14 months: 9/237 (4%), 26 months: 7/171 (4%), 38 months: 2/120 (2%)				with a treatment period of 38 months
Hagenacker 2020 ²¹²	Germany	Multiple treatment centres	Prospective Before after	n = 173 6-month analysis Type 1 (2%), type 2 (36%), type 3 (62%) Mean age = 36 years 10-month analysis Type 1 (1%), type 2 (33%), type 3 (65%), type 4 (1%) Mean age = 37 years 14-month analysis Type 2 (35%), type 3 (65%) Mean age = 33 years	NA	Motor function	NA	Minimum treatment time of 6 months to a follow-up of up to 14 months
Hodgkinson 2021 ¹²⁵	Canada	National registry	Retrospective Controlled	n = 146	Treatment naïve	Motor function	NR	
Huang 2025 ²⁶⁹	China	Hospital	Prospective Before after	n = 49 Type 2 (67%), type 3 (33%)	NA	Motor function HRQoL Independence	Disease duration	18 months
Ip 2024 ¹⁸²	Hong Kong	EAP (Hong Kong); Multiple treatment centres	Prospective Before after	n = 23 Type 1 (35%), type 2	NA	Motor function	NA	Median follow-up of 3.4 years

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
				(30%), type 3 (35%) Median age = 5.8 years				
Jiang 2024 ²⁷⁰	China	Multiple treatment centres	Retrospective Before after	n = 50 Type 1 (20%), types 2/3 (80%) Median age = 4.6 years	NA	Adverse events Motor function	Age	2 years
Kariyawasam 2021 ¹⁸⁹	Australia	Treatment centre	Prospective Before after	n = 20 Type 1 (30%), type 2 (50%), type 3 (20%) Median age = 12 months	NA	Motor function	NA	Median 13.8 months (4–33.5)
Kolbel 2022 ²⁷¹	Germany	NR	Prospective Before after	n = 45 Type 1 or 2	Watchful waiting	Carer QoL	NA	NR
Konersman 2020 ¹⁹⁶	USA	Treatment centre	Retrospective Before after	n = 35 Type1 (11%), type 2 (40%), type 3 (37%)	NA	Motor function	NA	22 months
Kotulska 2022 ¹⁹¹	Poland	16 paediatric sites	Prospective Before after	Presymptomatic (1.4%) Type 1 (44%), type 2 (23%), type 3 (32%) Mean age = 6.9 years	NA	Motor function	Outcome measure CHOP-INTEND, HFMSE	1 year
Kroksmark 2023 ¹⁶⁶	Sweden	Treatment centre	Prospective Before after	N = 20 Type 2 (55%), type 3 (45%)	No formal comparator, but when nusinersen was approved, the patients were started on treatment, from youngest first. At baseline, none of the patients were treated with nusinersen, By follow-up, 10	Motor function Bone mineral density Biochemical assessments Nutritional status	NA	2 years

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
					had started treatment			
Krupa 2023 ²⁷²	Poland	Polish healthcare system	Retrospective Before after	n = 875 Presymptomatic (2%) Type 1 (25%), type 2 (24%), type 3 (49%)	NA	Time to death Ventilation	Later vs earlier treatment	2014-2022, 2019-2022. Assessments taken every year (2019, 2020, 2021, first five months of 2022)
Lavie 2021 ¹³²	Israel	SMA specialised referral centre	Retrospective Before after	n=20 Type 1	NA	Bulbar function Spinal deformities	NA	3 years
Le Goff 2023 ¹⁰⁵	France	Multiple treatment centres	Retrospective Before after	n = 41 Type 1 (54%), type 2 (46%) Age = 2.81 ± 0.82 years (type 1), 3.53 ± 0.73 years (type 2)	NA	Motor function	SMA type	Mean 17 months
Lee 2024 ²³⁵	South Korea	Treatment centres	Prospective Before after	n = 24 Type 2 (79%), type 3 (21%)	NA	Motor function Ventilation Feeding support Adverse effects Complications HRQoL ADL Caregiver burden	Sex Ventilator support Scoliosis Contracture SMA type	26 months
Lemska 2024 ²⁷³	Poland	Treatment centre	Prospective Before after	n=23 Type 1 (70%), type 2 (31%), type 3 (13%) Mean age = 31.09 months	NR	Motor function	NR	22 months
Li 2024a ¹²⁴	China	Treatment centre	Retrospective Case control	n=42 Type 2 (76%), type 3 (24%)	n = 42 healthy controls	Motor function	NR	6 months, 14 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
				Mean age = 57 months				
Li 2024b ²⁷⁴	China	Treatment centres	Retrospective Before after	n = 84 Type 1 (11%), type 2 (68%), type 3 (21%) Mean age = 6.47 years	NA	Motor function	NA	14 months
Li 2024c ²⁷⁵	International	FAERS database	Retrospective Before after	n=4807	NR	Adverse events	NR	NR
Li 2025 ¹⁰⁶	China	Hospital	Retrospective Before after	n = 42 Type 1 (29%), type 2 (62%), type 3 (9%)	NA	Motor function Adverse effects	Age	24 months
Lilien 2024 ²⁷⁶	International	Multiple treatment centres	Prospective Before after	n=99 Type 1, 2, 3 Median age = 11.2 years	NR	HRQoL	Non-responder Responder non-clinically significant Responder clinically significant	15 months
Lusakowska 2023 ¹⁸⁵	Poland	Treatment centres	Prospective Before after	n=20 Type 1 (10%), type 2 (16%), type 3 (74%)	NA	Motor function Adverse events	NR	30 months
Maggi 2020 ²⁰⁵	Italy	18 secondary or tertiary care centres	Retrospective Before after	n=116 Type 2 (11%), type 3 “sitters” (44%), type 3 “walkers” (45%)	NA	Motor function Respiratory function Adverse events	SMA type	6 and 14 months
Mendonca 2021a (Clinical) ¹³³	Brazil	Treatment centre	Prospective Before after	n = 21 Type 1	NA	Motor functions Nutritional support Respiratory support	NA	6-24 months
Mendonca 2021b (RWD) ²³⁴	Brazil	Treatment centre	Retrospective Before after	Nusinersen: Type 2 (47%), Type 3: (53%)	Control group Type 2 (44%), type 3 (46%)	Motor functions Hospitalisation	NA	12 and 24 months
Meyer 2021 ²³²	Germany	Treatment centres	Prospective Before after	n = 151 Type 1 (6%), type 2 (34%), type 3 (60%)	NA	Motor function Respiratory function ADLs	NA	No follow-up

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
Modrzejewsk a 2021 ¹⁸¹	Poland	Treatment centres	Prospective Before after	n = 26 Type 1 Median age = 23 months	NA	Motor function	NA	18-26 months
Moshe-Lilie 2020 ²¹⁵	NR	Chart review	Retrospective Before after	n = 22 Type 2 (41%), type 3 (59%) Median age = 36 years	NA	Motor function	NA	24 months
NICE 2020 ¹⁴³	UK	European registries	Prospective Before after	n = 168 Type 3 (non-ambulant) Adults and children	NA	Motor function	NA	NR
NICE-SMA study ¹²²	India	Treatment centre	Prospective Controlled before-after	SMA: n = 16 (nusinersen) n = 26 (standard of care) Type 2 (40%), type 3 (60%)	Natural history cohort: n = 72	Motor function QoL Adverse effects	NA	12 months
NURTURE ^{30,228}	International	Treatment centres	Prospective Before after	n=25 Presymptomatic Mean age = 20.5 days	NA	Motor function Respiratory function Adverse events	NA	5 years
Okamoto 2020 ¹⁸⁶	Japan	Treatment centres	Retrospective Before after	n=21 Type 1 (43%), type 2 (24%), type 3 (24%), type 4 (5%), unidentified (5%) Adults and children	NA	Motor function	NA	NR
Osmanovic 2021a ²³¹	Germany	Treatment centre	Prospective Before after	n= 28 Type 2 (46%), type 3 (50%), type 4 (4%) Median age = 36 years	NA	Motor function Treatment wearing	NA	34 months
Osmanovic 2021b ²¹⁰	Germany	Neuromuscular centres	Prospective Before after	n=31 Type 2 (36%), type 3 (59%), type 4 (5%) Mean age = 35.4 years	NA	Motor function Patient satisfaction	NA	2 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
Osredkar 2021 ¹⁷²	Slovenia/ Czech Republic	Treatment centres	Prospective Before after	Median age (range in years), 8.6 (0.2e18.8) Type 1 (26%), type 2 (52%), type 3 (21%)	NA	Motor functions	SMA type	14 months
Pane 2019 ¹³⁴	Italy	EAP (Italy)	Retrospective Before after	n=85 Type 1 2 months to 15 years	NA	Motor functions	NA	12 months
Pane 2021 ¹³⁵	Italy	EAP (Italy)	Prospective Before after	n = 122 Type 1 Mean age = 3.96 years	NA	Motor functions	Non-sitter Sitter	2 years
Pane 2022(iSMAC) ¹⁶⁸	Italy	Registry	Retrospective Before after	n=111 Type 2 (41%), type 3 (59%) Mean age = 12.51 years	Compared to untreated group but no information provided about characteristics of comparator	Motor functions	NA	24 months
Pane 2023 ¹³⁶	Italy	EAP (Italy)	Prospective Before after	n=48 Type 1 Mean age = 3.3 years	NA	Motor functions	NA	4 years (results from 2 years previously reported)
Pane 2024 ²⁷⁷	Italy	National registry	Prospective Before after	n = 75 Type 1 Nusinersen (n = 69) Switched to OA (n = 18) Switched to risdiplam (n = 5)	NA	Motor function Tube feeding	NA	12 months
Pechmann 2022 ¹⁷⁷	Germany/ Austria/ Switzerland	SMArtCare registry	Prospective Before after	n=256 Type 2 (85%), type 3 (15%) Mean age: Younger sitters: 30.8 months Older sitters: 120.9	NA	Motor functions Need for ventilator support Need for tube feeding Mortality Adverse events	Sitter types Number of copies	Maximum follow-up period of 38 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
				months Lost sitters: 98.5 months Lost walkers: 134.7 month				
Pechmann 2023a ¹³⁷	Germany/Austria/Switzerland	SMartCare registry	Prospective Before after	n = 88 (cohort 1) SMA type not reported Mean age = 8.4 months	n = 55 (cohort 2) Mean age = 89.8 months	Motor functions Need for ventilator support Need for tube feeding Mortality Adverse events	Sitter types Number of copies	Maximum follow-up period of 38 months
Pechmann 2023b ²⁰⁹	Germany/Austria/Switzerland	SMartCare registry	Prospective Before after	n = 231 Mean age: Pediatric walker: 103.3 months Adult walker: 443.5 months SMA type: Any type- Did not include type 3 who had lost ambulation	NA	Motor function Need for ventilator support Need for tube feeding Mortality Adverse events	Paediatric walkers Adult walkers	Up to 38 months follow-up
Peng 2025 ²⁷⁸	China	Hospital	Prospective Before after	n = 41 (with ≥6 months treatment) Type 1 (10%), Type 2 (73%), Type 3 (17%) Median age at treatment = 4.2 years	NA	Motor function Adverse effects	SMA types 1–3; Physical therapy vs no physical therapy	Baseline, 6, 10, and 14 months
Pera 2021 (iSMac) ²⁰³	Italy	Registry	Prospective Before after	n = 144 Type 3A (n = 74), Type 3B (n = 70) Age range = 30 months–68.27 years	NA	Motor function	Pediatric vs adult Sitters vs walkers Type 3A vs 3B	Mean follow-up = 1.83 years
Pinar 2024 ²⁷⁹	Turkey	Treatment centre	Prospective Before after	n = 37 Type 1 (41%), Type 2 (27%), Type 3 (32%)	NA	HFMSE, CHOP-INTEND; nutritional outcomes (HFA, BMI); malnutrition	SMA types 1, 2, 3	Before and after study period (2022–2023)

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
				Median age = 72 months (range 48–132)		screening scores (PYMS, STAMP)		
RESPOND ^{107,29}	NR	Treatment centre	Prospective Before after	n = 29	NA	Motor function Adverse effects	SMN2 copies	NR
Rich 2022 ¹⁴⁴	USA	Treatment centre	Retrospective Before after	n = 33 Type NR, adult SMA with 3+ SMN2 copies Mean age = 38.5 years	Control group (n = 6; limited data reported)	Serum and CSF NfL & pNfH; correlation with functional measures (RULM, HFMSE, SMAFRS, 6MWT)	Ambulatory (n = 13) vs non-ambulatory (n = 20)	Baseline, day 180, day 420
Sansone 2020 ¹³⁸	Italy	EAP (Italy)	Retrospective Before after	n = 118 Type 1 Median age = 42.8 months	NA	Respiratory function Carer perception of change	Age	6 months, 10 months
Sarikaya Uzan 2022 ¹⁹⁴	Turkey	Treatment centre	Retrospective Before after	n = 27 Type 1 (48.1%), Type 2 & 3 (51.8%) Median age = Type 1: 9.5 months, Type 2 & 3: 72 months	NA	CHOP-INTEND (Type 1), HFMSE (Type 2 & 3)	Type 1 vs Type 2 & 3	Up to 6 doses Two groups were followed up between September 2017 and June 2021
Scheijmans 2022 ¹⁸⁴	Netherlands	Treatment centre	Retrospective Before after	n = 71 Presymptomatic (3%), type 1 (32%), type 2 (42%), type 3 (23%) Median age = 54 months	NA	Motor function (CHOP-INTEND, HFMSE, HINE-2), respiratory and bulbar function, adverse events	Types 1b, 1c, 2a, 2b, 3a Presymptomatic subgroup	Median follow-up: 38 months (range 5–52 months) By type: Type 1b: 41 months, Type 1c: 45.5months, Type 2a: 34.5months, Type 2b:

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
								36months, Type 3a: 33.5months
Schneider 2021 ¹⁴⁵	Germany	Treatment centre	Prospective Before after	n = 15 Type 3 (100%) Median age = 36 years	Healthy controls (n = 15), ALS patients (n = 9)	RULM, HFMSE, Motor Unit Number (MScanFit), CMAP amplitude, D50 value	Walkers vs wheelchair users	4–8 months
Scoto 2018a ¹⁰⁸	UK	EAP (UK); single centre	Prospective Before after	n= 24 age range 3 months-9 years Type 1	NA	Motor function Adverse events	NA	NR
Scoto 2018b ¹⁰⁹	UK	EAP (UK); 17 centres	Prospective Before after	Type 1	NA	Motor function Need for ventilation	NR	Follow-up up to 5th injection
Shin 2023 ¹¹⁰	South Korea	Hospital	Retrospective Before after	N = 30 Age: 24.85 ± 8.59 (7.48–41.23) Age at first symptom onset: 1.16 ± 0.61 (0.5–3) Age at treatment: 22.90 ± 8.84 (4.98–39.5) Type 2 and 3 Type 2: 27/30 (90%) Type 3: 3/30 (10%)	NA	Motor function Adverse events	Some demographic details reported by SMA type Complications sub grouped by sex (male versus female) and SMA type (2 versus 3)	6, 14, 22 and 26 months
SHINE ^{35,120}	SHINE		Prospective Before after	n=207 Examining infantile and later-onset patients Median age 4.0 range 0.6 to 19.3 years Type 1 (expanded access programs had a common inclusion criterion of diagnosis of SMA type I)	All received nusinersen in SHINE- previously some participants had received sham procedure in ENDEAR and CHERISH studies	Motor functions Ventilation outcomes Hospitalisation HRQoL Adverse events		30 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
				SHINE included people with type 2 or type 3 SMA				
Simek 2024¹¹¹	Turkey	Hospital	Prospective Before after	n=31 Range: 19 to 69 years Types 2-4	NA	Motor functions HRQoL Respiratory function	NA	1.5 years
Simic 2024¹⁷³	Croatia		Prospective Before after	n = 30 Type 1 (43%), Type 2 (13%), Type 3 (30%) Median age = range 1 month–17 years	NA	CHOP INTEND and HFMSE scores CSF protein levels: t-tau, NfL, S100B	SMA types 1, 2, 3 and number of nusinersen doses	75–1275 days (average 675 days) Also reported as 18–24 months in some outcome analyses
Szabo 2020¹⁹⁵	Hungary		Retrospective Before after	n = 57; Type 1 (n = 13), Type 2 (n = 21), Type 3 (n = 23); mean age = 6.3 years (±5.4)	NA	Motor function, adverse events	SMA type, SMN2 copies, age at treatment	440 days (408 median)
Tachibana 2024²⁸⁰	Japan	Multiple treatment centres	Prospective Before after	n = 401; SMA SMA type: Infantile-onset: 126/401 (31.4%) Later-onset: 275/401 Type 2: 165/401 (41.1%) Type 3: 105/401 (26.2%)	NA	AEs, Clinical Global Impressions of Improvement (CGI-I) for effectiveness, HINE, 6MWT, HFMSE	SMA type	In patients with infantile-onset SMA, the mean duration of treatment was 383 days (SD 237 days) and the median duration of treatment

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
				Type 4: 5/401 (1.2%); Age at first nusinersen treatment > 0 - <3 months, n = 7 (1.7%) >3 - <6 months = 12 (3.0%) >6 - <12 months = 8 (2.0%) >12 - <24 months = 21 (5.2%) >2 - <15 years = 197 (49.1%) >15 < 65 years = 142 (35.4%) >65 years = 13 (3.2%)				was 421 days (range 1–814 days). In patients with later-onset SMA, the mean duration of treatment was 297 days (SD 197 days) and the median duration of treatment was 288 days (range 1–823 days).
Trancho 2024 ¹⁴⁶	NR		Prospective Before after	n = 35; SMA group (n = 19), control group (n = 16); mean age SMA = 32.9 years	Age-matched control group	Bone mineral density, motor function, physical activity	Group (SMA vs control)	1.0 ± 0.3 years
Trucco 2023 ¹⁶²	Italy	Multiple treatment centres	Prospective Before after	n = 45 children n = 22 adults (treated) n = 11 adults (untreated) Types 2 and 3	NA	Bulbar function	Sitter/walker Children/adults Treated/untreated	2 years

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
Trucco 2024 ¹²³	Italy	Italian SMA network, US PNCr network, SMA REACH UK	Retrospective Controlled	n = 69 Type 2 (77%), type 3 (23%) Mean age = 9.1 (type 2), 9.9 (type 3)	n = 103 natural history control Mean age = 9.3 (type 2), 11.7 (type 3)	Motor function Respiratory function Comorbidities Anthropometric	NA	5 years
Trucco 2022 ¹¹²	Italy	Italian SMA network, US PNCr, UK SMA REACH	Retrospective Before after	n = 100 Type 2 (81%), type 3 (19%) Mean age = 8 years (type 2), 9.4 years (type 3)	NA	Respiratory	Age	5 years
Tscherter 2022 ¹⁹⁰	Switzerland		Prospective Before after	n = 44; Type 1 (n = 11), Type 2 (n = 21), Type 3 (n = 12); median age = varies by type (0.2–18.5 yrs)	NA	Motor function, feeding, ventilation, speech	SMA type, age at treatment, SMN2 copies	42 months
Tulinus 2020 ¹¹³	Sweden	Hospital	Retrospective Before after	n = 70	NA	Motor function	NA	NR
Unver 2024 ¹¹⁴	Turkey	Multiple treatment centres	Prospective Before after	n = 44 Presymptomatic	NA	Motor function Bulbar function	NA	NR
van der Heul 2020 ⁷³	Netherlands		Prospective Before after	n = 16; Type 1; palliative (n = 11), nusinersen (n = 5); median age = 52–63 days	Palliative care vs nusinersen	Feeding, swallowing, motor function	Treatment group	NR
Van der Woude 2024 ²⁸¹	Netherlands	Hospital	Prospective Before after	n = 46; Type 2a (n = 23), 2b (n = 9), 3a (n = 14); median age = 5.2 years	NA	Motor function (HFMSE item-level changes)	SMA subtype, motor function category	20 months
Vázquez-Costa 2022 ¹⁶⁹	Spain		Prospective Before after	n = 79; Type 2a (n = 22), Type 2b (n = 8), Type 3a (n = 23), Type 3b (n = 23), Type 4 (n = 3);	Nusinersen vs untreated	Motor function, respiratory, activities of daily living, adverse events	SMA type, motor function level, SMN2 copies	16 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
				mean age = 30.3 (non-treated), 33.4 years (treated)				
Vidovic 2023 ²⁰⁶	Germany		Prospective Before after	n = 23; Type 2 (n = 9), Type 3 (n = 14); mean age = 38.1 years	NA	Motor function, cognitive outcomes	SMA type	14 months
Vill 2021 ¹⁹⁷	Germany		Prospective Before after	n = 43; SMN2 copies: 2 (n = 17), 3 (n = 10), 4 (n = 14), 5 (n = 2); age = 0–24 months	NA	Motor function, electrophysiological outcomes	SMN2 copy number, treatment status	13 months
Wang 2024 ²⁸²	China	Multiple treatment centres	Retrospective Before after	n = 54; Type 2 (n = 9), Type 3 (n = 43), Type 4 (n = 2); mean age = 27.0 years	NA	Motor function, respiratory, electrophysiological outcomes, adverse events	SMA type, function level (sitters/walkers), SMN2 copies	10 months
Weaver 2021 ¹⁷⁰	USA		Retrospective Before after	n = 35; Type 1 (n = 15), Type 2 (n = 14), Type 3 (n = 6); mean age not reported (children only)	NA	HRQoL, family impact, communication, daily activities	SMA type, nusinersen treatment stage	24 months
Weber 2024 ²¹⁶	Germany		Prospective Before after	n = 39; Adults (n = 23), Children (n = 16); Type 2 (n = 22), Type 3 (n = 17); median age adults = 38.4 years, children = 10.0 years	NA	Grip strength, motor function	SMA type, age group, SMN2 copies	12 months
Weststrate 2021 ¹¹⁵	UK	Hospital	Retrospective Controlled	n = 28 Type 1	n = 38 treatment naïve Type 1	Bulbar function Ventilation Mortality	NA	NR
Weststrate 2022 ¹²⁷	UK		Retrospective Before after	n = 24; Type 1a (n = 3), Type 1b (n = 9), Type 1c (n = 12);	NA	Bulbar function, motor function, respiratory, feeding	SMA subtype, age at treatment	24 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
				median age = 11 months			initiation, SMN2 copies	
Wohnrade 2023²³³	Germany		Prospective Before after	n = 39; Type 2 (n = 13), Type 3/4 (n = 26); median age = 36 years (range 19–65)	NA	Motor function, HRQoL, activities of daily living, depression/anxiety, caregiver burden	SMA type, SMN2 copy number, mobility status	16 months
Wurster 2024¹¹⁶	Germany	Hospital	Prospective Before after	n = 42 Type 1 (5%), type 2 (36%), type 3 (57%), type 4 (2%)	NA	Respiratory function	SMA type Smokers vs non-smokers	Median 22.1 months
Yang 2023¹¹⁷	China	2 hospitals	Retrospective Observational cohort	n = 46 Type 1 (17%), type 2 (67%), type 3 (15%)	NA	Motor function Adverse effects	SMA type	NR
Yao 2024²⁸³	China	Pediatric SMA China Registry	Retrospective Before after	n = 385 Type 1 (11%), type 2 (56%), type 3 (33%) Median age: 42 months (type 1), 62.5 months (type 2), 20 months (type 3)	NA	Motor function Adverse effects	NA	14 months
Yasar 2024¹³⁹	Turkey	Turkish E-Nabiz patient database	Retrospective Before after	n = 29 Type 1 Mean age = 3.7 years	NA	Motor function Bulbar function Scoliosis Radiological assessments	NA	Mean 3.3 years (range 2 to 6 years)
Yildiz 2023¹¹⁸	Turkey	Hospital	Retrospective Before after	n = 46 Type 1 (39%), type 2 (33%), type 3 (28%)	NA	Motor function Bulbar function Adverse effects Ventilation Complications	SMA type Age	NR
Zaidman 2023¹¹⁹	USA	Unclear	Prospective Before after	n = 43 Types 2 and 3 Mean age = 37.1 years	NA	Motor function Respiratory function Adverse effects	NA	NR
Zhang 2024¹⁴⁷	International	FAERS database	Retrospective Before after	n = 12,124,854 reports (FAERS); type not	NA	Adverse events (safety)	Age (children vs adults)	88 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
				reported; majority children (37.3%); mean/median age not reported				

19.5 Appendix 5: Table of included studies for risdiplam

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Follow-up time
Brakemeier 2024 ¹⁵³	Germany	Treatment centre	Prospective Before after	n = 29 Type 2 (96%), type 3 (4%) Eligible: type 2 or 3 on risdiplam for 4+ months Mean age = 34.32 years	NA	Motor function Bulbar function	12 months
Cornell 2024 ¹⁵⁶	UK	SMA REACH	Retrospective Before after	n = 92 Type 1 (78%), type 2 (22%) Eligible: 2 months to <18 years Median age = 12 years Previously treated with nusinersen, risdiplam (trial), or olesoxime (trial)	NA	Adverse events Discontinuation	Median treatment duration 11 months
EAP (US) ¹⁵²	USA	Treatment centres	Prospective Before after	n = 155 Type 1 (47%), type 2 (53%) Eligible: >2 months Median age = 11 years Previously treated with nusinersen, OA, or both	NA	Adverse effects Discontinuation	Median treatment duration 4.8 months
FIREFISH ⁵⁴⁻⁵⁶	International	Treatment centres	Prospective Phase 2 Single arm Open label	n = 41 Type 1 Eligible: 1 month to 7 months Median age = 5.3 months	NA	Motor function Feeding Respiratory function Mortality Ventilation	36 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Follow-up time
Goedeker 2024 ¹⁴⁸	USA	Chart review at 3 centres	Retrospective Observational	n = 29 Type NR Eligible: Newborn screen or prenatal test Mean age = 8.5 months	NA	Motor function Feeding support Mortality Ventilation Adverse effects	NR
Hahn 2022 ¹⁵⁴	Germany	Treatment centres	Retrospective Single arm	n = 134 Type 1 (28%), type 2 (72%) Eligible: >2 months Mean age (type 1) = 13.5 years Mean age (type 2) = 29 years Previously received nusinersen or nothing	NA	Adverse effects Discontinuation	Mean treatment duration (type 1) 5 months Mean treatment duration (type 2) 3.4 months
JEWELFISH ^{61,62,284,285}	International	Treatment centres	Prospective Phase 2 Single arm Open label	n = 173 Type 1 (9%), type 2 (62%), type 3 (29%) Eligible: 6 months to 60 years Median age = 14 years Previously enrolled in MOONFISH or received nusinersen or olesoxime or AVXS-101	NA	Adverse effects Discontinuation	24 months
Nascimento 2024 ¹⁴⁹	Spain	Treatment centres	Retrospective Before after	n = 25 Type 2 Eligible: any with type 2 Mean age = 14.1 years	NA	Motor function Adverse effects	8 months
RAINBOWFISH ^{57,58,60}	International	Treatment centres	Prospective Phase 2 Single arm Open label	n = Presymptomatic 1 day to 6 weeks Median age = 26.5 days	NA	Motor function Mortality Ventilation Adverse effects	2 years
Sitas 2024 ¹⁵⁵	Croatia	Treatment centre	Prospective Before after	n = 31 Type 2 (48%), type 3 (52%) Eligible: treatment naïve	NA	Motor function Bulbar function Adverse effects HRQoL	Type 2 median duration 16 months (n = 3) and 30 months (n = 12)

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Follow-up time
				adults Median age = 30 years			Type 3 median duration 16 months (n = 16)
SUNFISH ^{47,49-53}	International	Treatment centres	Prospective Phase 3 RCT	n = 176 Type 2 (73%), type 3 (27%) Eligible: 2 – 25 years Mean age = 9.9 years (risdiplam) Mean age = 10.3 years (placebo) Non-ambulant	Placebo	Motor function Bulbar function Hospitalisation Respiratory function Mortality Adverse effects Independence	5 years
Weng 2024 ¹⁵⁰	China	Treatment centre	Prospective Before after	n = 20 Type 1 (10%), type 2 (90%) Eligible: type 1 and 2 Median age = 20.7 years	NA	Motor function Adverse effects Independence	3 years
Yu 2024 ¹⁵¹	International	FAERS database	Retrospective Before after	n = 1588 Type NR Eligible: patient reports linked to risdiplam	NA	Adverse effects	NA

19.6 Appendix 6: Table of included studies for mixed drugs

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Follow-up time
Ashrafi 2024¹⁵⁷	Iran	Treatment centres	Prospective Controlled	Risdiplam (n = 73) Type 2 (73%), type 3 (27%)	Nusinersen (n = 52) Type 2 (66%), type 3 (34%)	Motor function Adverse effects Mortality	6 months
Dabbous 2022¹⁵⁸	USA	Chart review	Retrospective Chart review	n = 30 Type 1 Nusinersen (n = 11) OA (n = 8) Nusinersen to OS (n = 5)	NA	Motor function Bulbar function	NR
Lee 2022¹⁶⁰	USA	Treatment centre	Retrospective Before after	OA (n = 23) Nusinersen (n = 1) Risdiplam (n = 1) Nusinersen to OA (n = 5) OA to risdiplam (n = 2) Prenatally identified	NA	Motor function Respiratory function Bulbar function	3 years
Mirea 2022¹⁵⁹	Romania	Treatment centre	Retrospective Before after	Age: 0-17 years Type 1: 20 Type 2: 26 Type 3: 9	As not all patients could attend daily PT- due to location, sample was split into two groups: Nusinersen and PT (PT-N) compared to Nusinersen only (N group) Nusinersen administered the same in both groups- addition of PT in PT-N group	Motor function	12 months

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19.7 Appendix 7: Summary of included cost-effectiveness analysis studies

Table 131: Summary of the economic analyses included in the original systematic review and updated review

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
Original systematic review (up to January 2024)						
NICE- Nusinersen TA588, 2019²	Target population: Paediatric patients with 5q SMA (Types 1,2 and 3) Subgroups: 1- infantile Infantile-onset (type 1) • ≤12 weeks disease duration • >12 weeks disease duration 2- Later-onset ((types II and III) SMA.) • <25 months disease duration • ≥25 months disease duration	Intervention: Nusinersen Comparator: BSC Outcomes: LYG, QALYs Study perspective: NHS and PSS of UK Location (Setting): UK (relevant settings (e.g. inpatient, outpatient/clinic))	Two Markov models: • Infantile onset (type 1) • Later-onset (type 2/3) Health states: Type 1: Eight health states based on HINE-2 including: No milestone achieved, mild milestones, moderate milestones, sits without support, stands with assistance, walks with assistance, stands/walks unaided and dead. Type 2/3: Seven states based on HMFSE and WHO	Time horizon: • Type 1: 60 years • Type 2/3: 80 years Cycle length: • Type 1: new cycle after 2, 6, 10, 13 and 14 months and every 4 months thereafter • Type 2/3: new cycle after 3, 6, 9, 12 and 15 months and every 4 months thereafter Discount rate: • 3.5% per year for both costs and benefits	Patients: Patients (type 1 and type 2/3) had utility values determined by manufacturer experts. Caregiver: Caregiver disutilities were based on Spanish caregiver data and UK population EQ-5D scores. It was assumed that type 1 patients had 3 caregivers, while type 2/3 patients had 2 caregivers, with 3 for those unable to sit.	Sources of costs: • Real-World Evidence (RWE) survey to validate the direct expenses linked to SMA within the UK healthcare system (2017 RWE survey involving pediatric neurological consultants from nine UK centers). • Analyzed data from the Hospital Episode Statistics (HES) in the UK Currency and conversion: UK pound (£)

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
			including: Sits without support but does not roll, sits and rolls independently, sits and crawls with hands and knees, stands/walks with assistance, stands unaided, walks unaided and dead.			
NICE-Risdiplam TA755, 2021³	Target population: • Paediatric patients with 5q SMA (Types 1,2 and 3) Subgroups: • Type 2/3: included both ambulant and non-ambulant patients aged 2–25 years at the time of enrolment with type 2 and 3 SMA. • Type 1: included infants with symptomatic type 1 SMA aged 1–7 months at the time of enrolment.	Intervention: Risdiplam Comparator: BSC Outcomes: LYG, QALYs Study perspective: NHS and PSS of UK Location (Setting): UK (relevant settings (e.g. inpatient, outpatient/clinic))	Two Markov models: • Type 2/3 model • Type 1 model Health states: Type 2/3: Six states based on MFM-32 and HMFSE ('not sitting', 'sitting with support', 'sitting unsupported', 'standing (with or without support)' and 'walking (with or without support)' and 'death'. (Plateau at 26 months)	Time horizon: • Type 1 and Type 2/3: 90 years Cycle length: • Type 1 and Type 2/3: one month. Discount rate: • 3.5% per year for both costs and benefits	Patients: Utility values same as NICE-nusinersen TA588.² Caregiver (type 1): Adjusted disutility assumption with no QALY losses post 10.23 years. Bereavement considered after 30.58 years. Assumed 2.2 caregivers per patient. Caregiver (type 2/3): Disutility linked to patient health states, caregiver utility returns to normal after patient death. Disutility of -0.04	Sources of costs: • Health state resource use for NICE-nusinersen TA588.² • Costs for permanent ventilation are 175% higher than non-sitting health states. • SMA complication costs apply universally in BSC and half in risdiplam groups in severe health states. • The costs per unit and occurrence rates for each complication were obtained from the NHS Reference Costs of 2019/20.

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
			Type 1: Six states based on HINE-2 ('not sitting', 'sitting', 'standing', 'walking') and 'permanent ventilation' and 'death'. (Plateau at 66 months)		applied for 20 years (scenario 1) and 90 years (scenario 2) after patient's death.	Currency and conversion: UK pound (£)
NICE-OA HST15-type1, 2021²⁵⁶	patients with 5q SMA- Infantile-onset (type 1)	Intervention: Onasemnogene abeparvovec Comparator: BSC Outcomes: LYG, QALYs Study perspective: NHS and PSS of UK Location (Setting): UK (relevant settings (e.g. inpatient, outpatient/clinic))	One Markov model Health states: Six states: not sitting, permanent assisted ventilation, sits unassisted, walks unassisted, within a broad range of normal development and dead.	Time horizon: 100 years Cycle length: 6-month cycles for first 3 years, 12-month cycles for remainder of model Discount rate: • 3.5% per year for both costs and benefits	PAV: Assumption based on the ERG interim report Not sitting – BSC and onasemnogene abeparvovec: Thompson et al. 2017²⁸⁶ Sits unassisted – BSC and onasemnogene abeparvovec: TA588² Walks unassisted and Broad range of normal development: Ara and Brazier 2010²⁸⁷	Sources of costs: Inpatient and outpatient costs: NHS pharmacological therapy resources: PCA Currency and conversion: pound (£)-2019

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
NICE-OA HST24-presymptomatic, 2023¹⁶	Newborn infants with genetically confirmed, presymptomatic SMA with two or three copies of the <i>SMN2</i> gene who were age ≤6 weeks (≤42 days) at time of treatment.	Intervention: Onasemnogene abeparvovec Comparator: BSC Outcomes: LYG, QALYs Study perspective: NHS and PSS of UK Location (Setting): UK (relevant settings (e.g. inpatient, outpatient/clinic))	Two Markov model: • Short-term model • Long-term extrapolation model Health states: Short-term: Six states including: 'Sitting and walking independently', 'non-sitter, no PAV', 'non-sitter, PAV', 'sitter', 'delayed walker', 'death' Long-term: Seven states including six states from short term and 'experiences later onset SMA'	Time horizon: 100 years Cycle length: One month Discount rate: • 3.5% per year for both costs and benefits	PAV: Assumption based on the ERG interim report Not sitting and Patients in the walking & experiencing later onset SMA state who lose the ability to walk: Thompson et al. 2017²⁸⁶ Sitting: EAG's clinical experts in TA588² Walking and broad range of normal development: Ara and Brazier 2010²⁸⁷	Sources of costs: Costs sourced from NHS 2019/20, the NHS Business Services Authority prescription cost analysis 2021/22, and the literature. Currency and conversion: UK pound (£) inflated to 2021
ICER-Nusinersen & OA, 2019²⁴³	SMA patients of all ages and types including: • symptomatic patients with infantile-onset (Type I) SMA	Intervention: Nusinersen and onasemnogene abeparvovec Comparator: BSC	Three de novo Markov models in accordance with target population. Health states:	Time horizon: Lifetime Cycle length: One month	PAV for both arms, Not sitting for BSC arm: Thompson et al. 2017²⁸⁶ Not sitting for treatment arm: Assumption	Sources of costs: Nusinersen: Drug: Redbook 2018²⁸⁸, Magellan 2016²⁸⁹ Inpatient Cost: Nationwide

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
	• symptomatic patients with later-onset (Type II/III) SMA • presymptomatic SMA patients	Outcomes: LYG, QALYs Study perspective: USA health care sector Location (Setting): USA (inpatient, outpatient/clinic, office, and home settings)	• Type I and Presymptomatic models: 'Not sitting', 'PV', 'sitting', 'walking', 'death' • Type II/III: 'sitting', 'walking', 'death' Absorbing states For long-term extrapolation model: Type I: 'PV' and 'death' Type II/III: 'death'	Discount rate: 3.0% for costs and benefits	Sitting for BSC arm: TA588² Sitting for treatment arm: Assumption Walking for both arms: General population utility	Children's Hospital Price Information List 2018 Onasemnogene abeparvovec Drug cost: Market analyst Estimate²⁹⁰ Administration costs for both arms: Physician fee schedule 2018²⁹¹; Facility price Redbook 2018²⁸⁸ Currency and conversion: \$US inflated to 2017
CADTH-Nusinersen, 2019²⁵³	Patients with SMA (type 1, 2 and 3)	Intervention: Nusinersen Comparator: RWC Outcomes: LYG, QALYs Study perspective: Canadian public health care system	Three Markov models: type I, type II, and type III Health states: • Type I: 'baseline'; 'improved baseline'; 'worsened baseline'; 'no improvement'; 'sits without support';	Time horizon: • type 1: 25 years • type 2: 50 years • type 3: 80 years Cycle length: • type 1: At 2, 6, 10, 13, and 14 months. Subsequent	Patient: Types 1 and 3 SMA: unpublished utility value analyses by five experts in SMA Type 2 SMA: QoL data from CHERISH mapped to EQ-5D	Sources of costs: Health costs appear to be derived from a study of SMA costs in Germany (Klug et al., 2016)²⁶¹. Currency and conversion: Canadian dollars for 2017

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
		Location (Setting): Canada	'stands with assistance', 'walks with assistance', 'stand/walks unaided', 'loss of type II/III motor function', and 'death'. • Type II: 'baseline', 'worsened', 'no', 'mild' and 'moderate' improvement, 'stand/walk with assistance', 'stand unaided', 'walks unaided', 'loss of ambulation with/without assistance' and 'death'. • Type III: 'baseline', 'non-ambulatory', 'ambulatory', and 'death'.	cycles were every four months. • type 2: three months (For the first 15 months). Subsequent cycles were every four months. • type 3: three months (for the first 27 months), subsequent cycles every 4 months. Discount rate: 1.5% costs and benefits per annum		
CADTH-risdiplam , 2021²⁵⁵	population was divided into two subgroups evaluated separately:	Intervention: Risdiplam Comparator: BSC	Two Markov models in accordance with target population. Health states:	Time horizon: • Type I: 25 years • Type II/III: 80 years	Health state utility values were obtained from a sponsor-commissioned Canadian burden-of-	Sources of costs: Outpatient, hospitalizations, Medical equipment and medications identified from a

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
	- patients with SMA type I - patients with SMA type II or SMA type III	Outcomes: QALYs Study perspective: Canadian publicly funded health care payer Location (Setting): Canada	Type I: six states including 'not sitting', 'sitting', 'standing', 'walking', 'permanent ventilation', and 'death' Type II/III: 'not sitting', 'supported sitting', 'unsupported sitting', 'standing', 'walking', and 'death'	Cycle length: For both models one month Discount rate: 1.5% costs and benefits per annum.	illness survey. (included a EuroQol 5-Dimensions 5-Levels health utility questionnaire). In the absence of available data for the "PV" and "not sitting" states, the value identified in the survey for sitting supported was applied to both health states.	Canadian burden-of-illness study. Health care resource utilization come from the Alberta Hospital, the Ontario Ministry of Health 2020. End-of-life costs were obtained from Widger et al.²⁹² and Seow et al.²⁹³ Currency and conversion: Canadian dollars
CADTH-OA, 2021 ²⁴⁴	Patients with SMA type 1 with an onset of symptoms at ≤ 6 months of age, and with 2 copies of the SMN2 gene.	Intervention: Onasemnogene abeparvovec Comparator: BSC and Nusinersen Outcomes: QALYs Study perspective: Canadian publicly funded health care payer	One Markov model Health states: six states including: 'within a broad range of normal development', 'walking unassisted', 'sitting unassisted', 'unable to sit unassisted', 'PAV' and 'death'	Time horizon: 60 years Cycle length: Six 6 months in the early phase and yearly in the extrapolation phase. Discount rate: 1.5% costs and benefits per annum.	Utility for the 'unable to sit unassisted' and 'sitting unassisted' health states was identified from the literature (TA588)² utility of the general population for the 'walking unassisted' and 'within broad range of normal development' health states were derived from (Ara et al, 2010)²⁸⁷	Sources of costs: - Administration costs: Ontario Schedule of Benefits for physician services. - Screening costs: expert opinion. - Health state costs: unpublished health care resource utilization study conducted by the sponsor.

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
		Location (Setting): Canada				Currency and conversion: Canadian dollars
Meijer et al., 2023²⁴⁸	Patients with SMA Type I, SMN1 mutation, 2 SMN2 copies, treated before 6 months	Intervention: Onasemnogene abeparvovec Comparator: BSC Outcomes: QALY Study perspective: Societal perspective Location (Setting): Netherlands	One Markov model Health states: five health states including: 'not sitting and 'PAV free', 'PAV', 'sitting independently', 'walking independently', and 'dead'.	Time horizon: 36 months for short-term and 99 years for long-term Cycle length: monthly Discount rate: 4% for costs and 1.5% for benefits	Literatures (mainly ZIN report of nusinersen and the comments provided in the ZIN report of Onasemnogene abeparvovec)	Sources of costs: Literature (study conducted by Klug et al. in Germany in 2016) ²⁶¹ Currency and conversion: € and adjusted for 2022
Broekhoff et al., 2021²⁴⁵	Infants born with SMA I- Mean age (months) = 3.4	Intervention: OA Comparator: BSC and nusinersen Outcomes: QALYs Study perspective: societal perspective Location (Setting): Netherlands	One Markov model Health states: five health states: three states corresponding to SMA types (SMA I-III), one for PV, and one for death.	Time horizon: 100 years Cycle length: one month. Discount rate: 4% for Costs and 1.5% for benefits	The base-case model utilized health state utilities sourced from the Dutch National Health Care Institute (ZIN) model, while a scenario analysis incorporated utilities from the Institute for Clinical and Economic Review (ICER Institute).	Sources of costs: published literature (the ZIN report, which uses cost calculations by Klug et al.) ²⁶¹ Currency and conversion: Euro € and were inflated to 2019

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
SMC Nusinersen, 2018²⁵⁴	patients with symptomatic type 1 SMA	Intervention: Nusinersen with BSC Comparator: BSC Outcomes: QALY, YLG Study perspective: NHS Scotland and social work Location (Setting): Scotland	Two Markov models (type I SMA and type II or III SMA) Health states: A 10-state Markov model tracks infant patients' health progression through worsening, stabilizing, improving states, and functional milestones like 'sitting without support' or 'standing without assistance.' The model for later-onset SMA patients mirrors the infant model but includes state adjustments tailored to type II and III SMA.	Time horizon: 80 years Cycle length: Unclear Discount rate: Unclear- it seems %3 for cost and outcome	Health state utilities in the later-onset model were derived by converting PedsQL data from the CHERISH study to EQ-5D. Infantile model values were adjusted from later-onset utilities to reflect infant-specific characteristics.	Sources of costs: Unclear Currency and conversion: £2018
SMC OA , 2021²⁵⁷	patients with SMA with a bi-allelic mutation in the SMN1 gene (or up to 3 copies of the SMN2 gene) and a	Intervention: Onasemnogene abeparvovec	One Markov models Health states: Six states including 'normal	Time horizon: lifetime Cycle length: six months for the	utility values were sourced from the literature using proxy parental or carer values and/or clinical advice.	Sources of costs: Scottish Health Service Costs where available

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
	clinical diagnosis of SMA type 1.	Comparator: Nusinersen Outcomes: QALY, LYG Study perspective: health and social care Location (Setting): Scotland	development' , 'unassisted walking' , 'unassisted sitting' , 'inability to sit' , 'reliance on assisted ventilation' , and 'death'	first three years and annually thereafter Discount rate: Unclear- it seems 3% for cost and outcome		Currency and conversion: pound and for 2020
SMC Risdiplam, 2022²⁵⁹	Infants with symptomatic type 1 SMA aged 2–7 months were used in the type 1 model, while the type 2/3 model included ambulant and non-ambulant patients aged 2–25 years.	Intervention: Risdiplam with BSC Comparator: Nusinersen with BSC Outcomes: QALY Study perspective: Unclear (maybe payer and social perspective) Setting: Unclear Location: Scotland	Two Markov models: (type I SMA and type II or III SMA) Health states: Both models utilized a six-state Markov model with common motor milestone states: not sitting, sitting, standing, and walking. The type 2/3 model distinguished the 'sitting' state into 'with' and 'without support'. Type 1	Time horizon: lifetime Cycle length: one month Discount rate: Unclear	Patient and caregiver utility data for motor milestone health states in Type 1 and Type 2/3 models were sourced from literature or NICE submission TA588 ² .	Sources of costs: Costs for drug acquisition, administration, and resource use of risdiplam and nusinersen were factored in from real-world studies by their respective companies.

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
			model included a 'permanent ventilation (PV)' state. Death was the absorbing state in both models.			
Connock et al., 2020²⁴⁶	Patients with SMA Type 1	Intervention: Onasemnogene abeparvovec Comparator: BSC and nusinersen Outcomes: QALY Study perspective: UK NHS perspective Location (Setting): UK	One Markov model Health states: Unclear	Time horizon: Lifetime Cycle length: Unclear Discount rate: Maybe 3.5% for both costs and benefits	Total lifetime QALYs for nusinersen, onasemnogene abeparvovec come from Table 8 Malone et al. 2019 ²⁵⁸ Total lifetime QALYs for BSC and nusinersen come from Biogen submission to NICE (2018) ³¹	Sources of costs: Total lifetime costs for nusinersen and onasemnogene abeparvovec come from Malone et al. 2019 ²⁵⁸ Total lifetime costs for BSC and nusinersen come from Biogen submission to NICE (2018) ³¹ Currency and conversion: £UK using 2018 PP exchange rate
Dean et al. , 2021²⁴⁷	Symptomatic SMA type 1 patients	Intervention: Onasemnogene abeparvovec Comparator: Nusinersen, BSC	ONE Markov model Health states: The states of the model are like the "ICER -	Time horizon: Lifetime Cycle length: 6-monthly for first 3 years then annually	Equivalent to weightings used in the ICER analysis ²⁴³	Sources of costs: Price of onasemnogene abeparvovec \$2.125 M one-time dose, other costs were equal to costs used in the ICER analysis

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
		Outcomes: QALY Study perspective: Commercial payer OF USA Location (Setting): USA	nusinersen & OA 2019” study ²⁴³ Markov model for Type I SMA.	Discount rate: 3% for both costs and benefits		(2019) ²⁴³ , cost of ventilator estimated from a UK study(Noyes et al. 2006) ²⁹⁴ Currency and conversion: \$US inflated to 2017
Malone et al., 2019 ²⁵⁸	Paediatric with genetically confirmed SMA1 and two copies of SMN2, diagnosed before six months of age, and receiving either the recommended therapeutic amount of onasemnogene abeparvovec or nusinersen, along with BSC	Intervention: Onasemnogene abeparvovec Comparator: Nusinersen Outcomes: QALY, LYG Study perspective: Commercial insurer in the U.S. Location (Setting): USA	ONE Markov model Health States: ‘Within a broad range of normal development’, ‘Walking functionally equivalent to SMA Type III’ , ‘Sitting functionally equivalent to SMA Type II’ , ‘Not sitting and living ventilation-free’ , ‘Not sitting and requiring permanent assisted ventilation’ , and ‘Death’	Time horizon: 100 years Cycle length: six months for the first three years, and then 12 months for all cycles thereafter Discount rate: 3% for both costs and benefits	The model incorporated utility values derived from the CHERISH (PedsQL data) clinical trial of nusinersen for later-onset SMA (NCT02292537), which were transformed to the EQ-5D youth version through a documented algorithm. ²⁸⁶	Sources of costs: SMA patient costs in USA: commercial plans by age at first claim. ²⁹⁵ Nusinersen product cost: based on manufacturer ³¹ nusinersen administration cost: Micro-costed. Hospital mark-up component and Durable medical equipment: expert opinion Hospital stays for anesthesia-related complications: Graham et al. ²⁹⁶

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
						Currency and conversion: \$US, price year is unclear
Wang et al. 2022²⁴⁹	infants born with SMA Type I as the recruited patients in the clinical trials of nusinersen and onasemnogene abeparvovec	Intervention: Onasemnogene abeparvovec Comparator: SOC and nusinersen Outcomes: QALY Study perspective: healthcare system in the Australian context Location (Setting): Australian	ONE Markov model Health states: Five health states in including: 'not sitting and PAV free', 'sitting independently', and 'walking independently' and 'dead'	Time horizon: 100 years Cycle length: Monthly Discount rate: 5% annually for both costs and benefits	Utility values come from Chambers et al.2020 ²⁹⁷	Sources of costs: Treatment costs of nusinersen: PBS²⁹⁸ Treatment costs of onasemnogene abeparvovec: Market price Administration and monitoring costs of nusinersen and onasemnogene abeparvovec: PBS²⁹⁸, MBS²⁹⁹, NHDC³⁰⁰ Health state costs: Recently published study in Australia²⁹⁷ AND ICER²⁴³ Currency and conversion: \$ Australian were converted to 2020

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
Zuluaga et al. 2019²⁵⁰	Patients with infantile-onset and later-onset SMA	Intervention: Nusinersen and SoC Comparator: SoC Outcomes: QALY Study perspective: societal Location (Setting): Sweden	Two Markov model (infantile-onset SMA and later-onset SMA) Health states: infantile-onset: ten states including: 'baseline', 'Worsened', 'stabilisation of baseline' and 'Improved', 'Stands/walks Unaided', 'Sits Unaided', 'Stands aided', 'Walks aided', 'Loss of later-onset motor function', 'Death' Later-Onset: 'baseline', 'Worsened', 'Stabilised', 'Mildly improved', 'Moderately improved', 'Stands unaided', 'Walks unaided', 'Stands/walks with assistance', 'Loss of ambulation with/without	Time horizon: 40 years for infantile-onset and 80 years for later-onset Cycle length: In trial follow-ups for ENDEAR: days 1, 64, 183, 302 and 394; CHERISH: days 1, 92, 169, 274, 365 and 456; after follow-ups: four months Discount rate: 3.0% for both costs and benefits	Health-state utility values come from Lloyd et al. 2017 ³⁰¹ The EQ-5D (youth version) was scored using the EQ-5D-3L UK preference weights.	Sources of costs: German study (Klug et al. 2016)²⁶¹ and a Spanish study (López-Bastida et al. 2017)⁶⁶ Country-specific unit costs were mainly collected from hospital price lists. Currency and conversion: SEK (Swedish krona)-inflated to the year 2018

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
			assistance', 'Death'			
Thokala et al. 2020²⁵¹	patients with infantile-onset SMA (type 1)	Intervention: Nusinersen Comparator: BSC Outcomes: LYG, QALY Study perspective: US health care sector Location (Setting): US	One Markov model The model contained two parts: (1) a short-term phase concordant with clinical study data, and (2) a long-term extrapolation model. Health states: 'permanent ventilation', 'not sitting', 'sitting', 'walking', and 'death'.	Time horizon: lifetime Cycle length: monthly Discount rate: 3% per annum for both costs and benefits	Permanent ventilation for both arms: Thompson et al., 2017 ²⁸⁶ (EQ-5D) Not sitting in BSC arm Same as "permanent ventilation" and for Nusinersen based on assumption Sitting for BSC based on TA588 ² and for Nusinersen based on assumption	Sources of costs: Nusinersen treatment cost: Magellan 2016 ²⁸⁹ , Redbook 2018 ²⁸⁸ Administration cost: Physician fee schedule 2018 ²⁹¹ ; Nationwide Children's Hospital The health care utilization costs: Shieh et al. 2017 ²⁹⁵ Currency and conversion: \$US-inflated to 2017
NCPE-2017²⁵²	infantile and later onset SMA	Intervention: Nusinersen Comparator: SOC Outcomes: QALY, LYG Study perspective: Health Service Executive	Two Markov models (infantile and later onset SMA) Health states: Unclear	Time horizon: Lifetime Cycle length: determined by motor assessments timing and maintenance dose administration.	PedsQL data from CHERISH trial determined later-onset SMA utilities, impacting infantile SMA model. Data mapped to EQ5D scale for utility derivation.	Sources of costs: Unclear Currency and conversion: Euro(€)

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
		Location (Setting): Ireland		Discount rate: % for costs and benefits		
Systematic review update						
Khuntha et al, 2025²⁴²	Infantile, SMA type 1, 2 and 3	Intervention: Onasemnogene Abeparvovec, Risdiplam Comparator: SOC Outcomes: QALY, LYG Study perspective: Thai health care system Location (Setting): Thailand	One Markov models: (SMA type 1, 2 & 3)	Time horizon: Lifetime Cycle length: 6 months Discount rate: 3.0% for both costs and benefits	"The EuroQol Five-dimension Youth (EQ-5D-Y) which used the published tariff from Japan (Shiroiwa et al., 2021 for health states BRND, sitting and PAV. Other health state utility values from a percentage of the difference between each health state from Hu et al., 2022 - the Chinese EQ-5D-Y using data from the Chinese EQ-5D-3L valuation study as a proxy.	Sources of costs: Hospital, Pharmaceutical drug assessment submissions and direct interviews of patients and caregivers.
Abbreviations: BSC = best supportive care; LYG = life-year gained; PSS = personal social service; QALY = quality adjusted life-year; RWE = real-world evidence; SMA = spinal muscular atrophy; OA = Onasemnogene abeparvovec; PCA = pharmacological therapy resources; PAV = permanent assisted ventilation; PPP = purchasing power parity; SOC = Standard Of Care; PBS = Pharmaceutical Benefits Scheme; MBS = Medicare Benefits Schedule; NHCDC = National Hospital Cost Data Collection						

19.8 Appendix 8: Reporting quality assessment of economic studies

The reporting quality of studies assessed in the original systematic review are provided in Table and Table . Additionally, assessment of the reporting quality of the one study included in this review update is provided in Table .

Table 132: Reporting quality of the economic evaluations in the original systematic review using the CHEERS checklist (Part I)

CHEERS criteria	Study and location where item is reported (page for location refer to PDF page)									
	NICE-Nusinersen TA588	NICE-Risdiplam TA755	NICE-Onasemnogene HST15-type1	NICE-Onasemnogene HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam 2021	CADTH Onasemnogene -2021	Meijer 2023	Broekhoff-2021
Title										
Identify the study as an economic evaluation and specify the interventions being compared	Yes	Yes	Yes	Yes	Yes P:1	Yes P:1	Yes P:1	Yes P:1	Yes P:1	Yes P:1
Abstract										
Provide a structured summary that highlights context, key methods, results, and alternative analyses.	No	No	No	No	Yes P:8	Yes P:6-7	Yes P:168-169	Yes P:7-9	Yes P:3	Yes P:1
Introduction										
Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	No	Yes	Yes	Yes	Yes P:49-61	Yes P:8-10	Yes P:25-30, 44-47	No	Yes P:8-13	Yes P:1-2
Methods										
Health economic analysis plan: Indicate whether a health economic analysis plan was developed and where available.	No	No	No	No	No	No	No	No	No	No
Study population: Describe characteristics of the study population (such as age range, demographics,	Yes	Yes	Yes	Yes	Yes P:101	Yes P:12	Yes P:168	Yes P:11	Yes P:14	Yes P:4

CHEERS criteria	Study and location where item is reported (page for location refer to PDF page)									
	NICE-Nusinersen TA588	NICE-Risdiplam TA755	NICE-Onasemnogene HST15-type1	NICE-Onasemnogene HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam 2021	CADTH Onasemnogene -2021	Meijer 2023	Broekhoff-2021
socioeconomic, or clinical characteristics).										
Setting and Location: Provide relevant contextual information that may influence findings.	Yes	Yes	Yes	Yes	Yes P:57	Yes P:2	Yes P:2	Yes P:2	Yes P:14	Yes P:4
Comparators: Describe the interventions or strategies being compared and why chosen.	Yes	Yes	Yes	Yes	Yes P:55	Yes P:9	Yes P:168	Yes P:7	Yes P:14	Yes P:4
Perspective: State the perspective(s) adopted by the study and why chosen.	Yes	Yes	Yes	Yes	Yes P:27	Yes P:12	Yes P:172	Yes P:7	Yes P:14	Yes P:4
Time Horizon: State the time horizon for the study and why appropriate.	Yes	Yes	Yes	Yes	Yes P:29	Yes P:12	Yes P:168	Yes P:7	Yes P:15	Yes P:4
Discount Rate: Report the discount rate(s) and reason chosen.	Yes	Yes	Yes	Yes	Yes P:27	Yes P:12	Yes P:172	Yes P:11	Yes P:15	Yes P:4
Selection of outcomes: Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Yes	Yes	Yes	Yes	Yes P:56	Yes P:12	Yes P:168	Yes P:7	Yes P:15	Yes P:4-5
Measurement of outcomes: Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Yes	Yes	Yes	Yes	Yes P:11	Yes P:15-16	Yes P:174-175	Yes P:13	Yes P:22-23	No
Valuation of outcomes: Describe the population and methods used to measure and value outcomes.	Yes	Yes	Yes	Yes	Yes P: 11	Yes P:15-16	Yes P:174	Yes P:13	Yes P:22-23	Yes P:4-5
Measurement and valuation of resources and costs: Describe how costs were valued.	Yes	Yes	Yes	Yes	Yes P: 111-115	Yes P:13	Yes P:174-175	Yes P:13	Yes P:23-25	Yes P:5

CHEERS criteria	Study and location where item is reported (page for location refer to PDF page)									
	NICE- Nusinersen TA588	NICE- Risdiplam TA755	NICE- Onasemnogene HST15-type1	NICE- Onasemnogene HST24- presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen- 2019	CADTH Risdiplam 2021	CADTH Onasemnogene -2021	Meijer 2023	Broekhoff- 2021
Currency, price date, and conversion: Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Yes	No	Yes	Yes	Yes P:11-115	Yes P:14	No	No	Yes P:23	Yes P:5
Rationale and description of model: If modelling is used, describe in detail, and why used. Report if the model is publicly available and where it can be accessed.	yes	yes	Yes	Yes	Yes P:99-101	No	Yes P:171	Yes P:11	Yes P:15- 16	No
Analytics and assumptions: Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Yes	Yes	Yes	Yes	Yes P:102-103	No	Yes P:171-174	Yes P:20	Yes P:36- 37	Yes P:5
Characterizing heterogeneity: Describe any methods used for estimating how the results of the study vary for subgroups.	Yes	Yes	Yes	Yes	Yes P:106-109	Yes 30-31	Yes P:171	Yes P:11	Yes P:12- 13	No
Characterizing distributional effects: Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Yes	Yes	Yes	Yes	Yes P:106-109	Yes P:14	Yes P:171	No	No	No
Characterizing uncertainty: Describe methods to characterise any sources of uncertainty in the analysis.	Yes	Yes	Yes	Yes	Yes P:115	No	Yes P:176-181	Yes P:14	Yes P:24- 26	Yes P:5-6
Approach to engagement with patients and others	Yes	Yes	Yes	Yes	Yes P:31	No	Yes P:30-34	Yes P:10	No	No

CHEERS criteria	Study and location where item is reported (page for location refer to PDF page)									
	NICE- Nusinersen TA588	NICE- Risdiplam TA755	NICE- Onasemnogene HST15-type1	NICE- Onasemnogene HST24- presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen- 2019	CADTH Risdiplam 2021	CADTH Onasemnogene -2021	Meijer 2023	Broekhoff- 2021
affected by the study: Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.										
Results										
Study parameters: Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Yes	Yes	Yes	Yes	Yes P: 117-136	No	No	Yes P:38	Yes P:25	Yes P:7
Summary of main results: Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Yes	No	Yes	No	Yes P:141-143	Yes P:14, 20	Yes P:182	Yes P:7, 24	Yes P:29	Yes P:5
Effect of uncertainty: Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Yes	Yes	Yes	Yes	Yes P: 117-136	No	Yes P:176-181	Yes P:25-26	Yes P:29- 32	Yes P:6-7
Effect of engagement with patients and others affected by the study: Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the	Yes	Yes	Yes	Yes	No	No	No	No	No	No

CHEERS criteria	Study and location where item is reported (page for location refer to PDF page)									
	NICE-Nusinersen TA588	NICE-Risdiplam TA755	NICE-Onasemnogene HST15-type1	NICE-Onasemnogene HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam 2021	CADTH Onasemnogene -2021	Meijer 2023	Broekhoff-2021
approach or findings of the study										
Discussion										
Study findings, limitations, generalizability, and current knowledge: Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Yes	Yes	Yes	Yes	Yes P:139-141	Yes P: 6, 15-19	Yes P: 169	Yes P:15-19, 26	Yes P:35-36	Yes P:9-10
Other										
Source of Funding: Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	No	No	No	No	Yes P:3	Yes P: 2	Yes P: 2	Yes P: 2	No	Yes P:10
Conflicts of Interest: Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Yes	Yes	Yes	Yes	Yes P:270-272	Yes P: 2	Yes P: 2	Yes P: 2	No	Yes P:10

Table 133: Reporting quality of the economic evaluations in the original systematic review using the CHEERS checklist (Part II)

CHEERS criteria	Study and location where item is reported (page for location refer to PDF page)									
	SMC Nusinersen-2018	SMC Onasemnogene -2021	SMC Risdiplam-2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sanchez et al. 2019	Thokala et al. 2020	NCPE-2017
Title										

CHEERS criteria	Study and location where item is reported (page for location refer to PDF page)									
	SMC Nusinersen- 2018	SMC Onasemnogene - 2021	SMC Risdiplam- 2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sanch ez et al. 2019	Thokala et al. 2020	NCPE-2017
Identify the study as an economic evaluation and specify the interventions being compared	No	No	No	Yes P:1	Yes P:1	Yes P:1	Yes P:1	Yes P:1	Yes P:1	Yes P:1
Abstract										
Provide a structured summary that highlights context, key methods, results, and alternative analyses.	No	No	No	Yes P:2	Yes P:1	Yes P:1	Yes P:1	Yes P:1	Yes P:1	No
Introduction										
Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Yes P:3-9	Yes P:2-8	Yes P:2-9	Yes P:2-3	Yes P:1-3	Yes P:1-2	Yes P:1-3	Yes P:1-3	Yes P:1-2	No
Methods										
Health economic analysis plan: Indicate whether a health economic analysis plan was developed and where available.	No	No	No	No	No	No	No	No	No	No
Study population: Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Yes P:11	Yes P:9	Yes P:10	Yes P:3	Yes P:1	Yes P:2	Yes P:2	Yes P:5	Yes P:2	No

CHEERS criteria	Study and location where item is reported (page for location refer to PDF page)									
	SMC Nusinersen- 2018	SMC Onasemnogene - 2021	SMC Risdiplam- 2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sanch ez et al. 2019	Thokala et al. 2020	NCPE-2017
Setting and Location: Provide relevant contextual information that may influence findings.	Yes P:1	Yes P:1	Yes P:1	Yes P:3	Yes P:1	Yes P:2	Yes P:2	Yes P:5	Yes P:2	Yes P:2
Comparators: Describe the interventions or strategies being compared and why chosen.	Yes P:11	Yes P:9	Yes P:10	Yes P:3	Yes P:3	Yes P:2	Yes P:3	Yes P:5	Yes P:2	Yes P:6
Perspective: State the perspective(s) adopted by the study and why chosen.	Yes P:11	Yes P:10	No	Yes P:3	Yes P:1	Yes P:2	Yes P:3	Yes P:5	Yes P:2	Yes P:5
Time Horizon: State the time horizon for the study and why appropriate.	Yes P:11	Yes P:10	Yes P:10	Yes P:3	Yes P:7	Yes P:2	Yes P:3	Yes P:5	Yes P:2	Yes P:5
Discount Rate: Report the discount rate(s) and reason chosen.	No	No	No	No	Yes P:7	Yes P:3	Yes P:3	Yes P:5	Yes P:2	Yes P:6
Selection of outcomes: Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Yes P:11	Yes P:11	Yes P:13	Yes P:3	Yes P:1	Yes P:2-3	Yes P:6	Yes P:5	Yes P:2	Yes P:1
Measurement of outcomes: Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Yes P:12	Yes P:10	Yes P:11	Yes P:3	Yes P:3	Yes P:6-7	Yes P:3	Yes P:13-14	Yes P:5-6	Yes P:5
Valuation of outcomes: Describe	Yes P:12	Yes P:10-11	Yes P:11	Yes P:3	Yes P:3-4	Yes P:6-7	Yes P:3	Yes P:13-14	Yes P:5-6	Yes P:5

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CHEERS criteria	Study and location where item is reported (page for location refer to PDF page)									
	SMC Nusinersen- 2018	SMC Onasemnogene - 2021	SMC Risdiplam- 2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sanchez et al. 2019	Thokala et al. 2020	NCPE-2017
the population and methods used to measure and value outcomes.										
Measurement and valuation of resources and costs: Describe how costs were valued.	No	Yes P:11	Yes P:11	Yes P:3	Yes P:3-4	Yes P:6	Yes P:3-4	Yes P:12-13	Yes P:6	No
Currency, price date, and conversion: Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Yes P:16	Yes P:16	Yes P:16	Yes P:3	Yes P:5	No	Yes P:4	Yes P:12	Yes P:6	No
Rationale and description of model: If modelling is used, describe in detail, and why used. Report if the model is publicly available and where it can be accessed.	No	No	No	No	No	Yes P:2-4	No	No	No	No
Analytics and assumptions: Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	No	No	No	No	No	Yes P:3	Yes P:3	Yes P:5	Yes P:2	No

CHEERS criteria	Study and location where item is reported (page for location refer to PDF page)									
	SMC Nusinersen- 2018	SMC Onasemnogene - 2021	SMC Risdiplam- 2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sanchez et al. 2019	Thokala et al. 2020	NCPE-2017
Characterizing heterogeneity: Describe any methods used for estimating how the results of the study vary for subgroups.	Yes	No	No	No	No	No	No	No	Yes P:7	No
Characterizing distributional effects: Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	No	No	No	No	No	No	No	No	No	No
Characterizing uncertainty: Describe methods to characterise any sources of uncertainty in the analysis.	No	No	No	No	No	Yes P:7	Yes P:5-6	Yes P:14	Yes P:7	Yes P:6
Approach to engagement with patients and others affected by the study: Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	Yes P:10	Yes P:8-9	Yes P:9-10	No	No	No	No	No	No	No
Results										

CHEERS criteria	Study and location where item is reported (page for location refer to PDF page)									
	SMC Nusinersen-2018	SMC Onasemnogene - 2021	SMC Risdiplam-2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sanchez et al. 2019	Thokala et al. 2020	NCPE-2017
Study parameters: Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	No	No	No	No	No	No	Yes P:4	Yes P:4-10	No	No
Summary of main results: Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Yes P:12-13	Yes P:11	Yes P:12	Yes P:2	Yes P:7	Yes P:9	Yes P:6	Yes P:15	Yes P:7	Yes P:6
Effect of uncertainty: Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Yes P:12-13	Yes P:12	Yes P:12	Yes P:4	Yes P:8	Yes P:10-11	Yes P:6-7	Yes P:14-17	Yes P:8-9	Yes P:6
Effect of engagement with patients and others affected by the study: Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to	No	No	No	No	No	No	No	No	No	No

CHEERS criteria	Study and location where item is reported (page for location refer to PDF page)									
	SMC Nusinersen- 2018	SMC Onasemnogene - 2021	SMC Risdiplam- 2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sanch ez et al. 2019	Thokala et al. 2020	NCPE-2017
the approach or findings of the study										
Discussion										
Study findings, limitations, generalizability, and current knowledge: Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Yes P:12-13	Yes P:13	Yes P:12-13	Yes P:4-5	Yes P:9-11	Yes P:11-12	Yes P:6, 8-9	Yes P:15-18	Yes P:9-10	No
Other										
Source of Funding: Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	No	No	No	Yes P:5	Yes P:11	Yes P:13	Yes P:9	Yes P:18	Yes P:11	No
Conflicts of Interest: Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	No	No	No	Yes P:5	Yes P:11	Yes P:12-13	Yes P:9	Yes P:18	Yes P:11	No

Table 134: Reporting quality of the economic evaluation in the systematic review update using the CHEERS checklist

CHEERS criteria	Location where item is reported (page for location refer to PDF page)
Title	
Identify the study as an economic evaluation and specify the interventions being compared	Yes P.1-2
Abstract	
Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Yes p.1
Introduction	
Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Yes p.1-2
Methods	
Health economic analysis plan: Indicate whether a health economic analysis plan was developed and where available.	No
Study population: Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Yes p.2-3; appendix 2 p5
Setting and Location: Provide relevant contextual information that may influence findings.	Yes p.3-4
Comparators: Describe the interventions or strategies being compared and why chosen.	Yes p.1-3
Perspective: State the perspective(s) adopted by the study and why chosen.	Yes p.3
Time Horizon: State the time horizon for the study and why appropriate.	Yes p.3
Discount Rate: Report the discount rate(s) and reason chosen.	Yes p.3
Selection of outcomes: Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Yes p.5
Measurement of outcomes: Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Yes p.5
Valuation of outcomes: Describe the population and methods used to measure and value outcomes.	Yes p.4-5
Measurement and valuation of resources and costs: Describe how costs were valued.	Yes p.4; Appendix 2, Table 6–9
Currency, price date, and conversion: Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Yes p.3
Rationale and description of model: If modelling is used, describe in detail, and why used. Report if the model is publicly available and where it can be accessed.	Yes p.2-3; appendix 1
Analytics and assumptions: Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Yes p4-5; appendix 3
Characterizing heterogeneity: Describe any methods used for estimating how the results of the study vary for subgroups.	No
Characterizing distributional effects: Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	No
Characterizing uncertainty: Describe methods to characterise any sources of uncertainty in the analysis.	Yes p.5; appendix 3
Approach to engagement with patients and others affected by the study: Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	Yes appendix 3
Results	

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Study parameters: Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Yes p5-4; appendix 2
Summary of main results: Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Yes p5-8
Effect of uncertainty: Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Yes p6-9
Effect of engagement with patients and others affected by the study: Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Yes p9
Discussion	
Study findings, limitations, generalizability, and current knowledge: Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Yes p.8-10
Other	
Source of Funding: Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Yes P.11
Conflicts of Interest: Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Yes P.11

19.9 Appendix 9: Methodological quality assessment of economic studies

The quality assessment of the economic evaluations included in the original systematic review are provided in Table and Table **Error! Reference source not found.** Additionally, the quality assessment of the study included in the systematic review update is provided in Table .

Table 135: Critical appraisal of the economic models in the original systematic review using an adapted Philips checklist (Part I)

Philips criteria		NICE-TA588	NICE-TA755	NICE-HST15-type1	NICE-HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam -2021	CADTH Onasemnogene - 2021	Meijer et al., 2023	Broekhoff et al., 2021
Structure											
1	Is there a clear statement of the decision problem?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Is the objective of the model specified and consistent with the stated decision problem?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Is the primary decision maker specified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear
4	Is the perspective of the model stated clearly?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	Are the model inputs consistent with the stated perspective?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6	Has the scope of the model been stated and justified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear
7	Are the outcomes of the model consistent with the perspective, scope and overall	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Philips criteria		NICE-TA588	NICE-TA755	NICE-HST15-type1	NICE-HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam -2021	CADTH Onasemnogene - 2021	Meijer et al., 2023	Broekhoff et al., 2021
	objective of the model?										
8	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
9	Are the sources of the data used to develop the structure of the model specified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10	Are the causal relationships described by the model structure justified appropriately?	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
11	Are the structural assumptions transparent and justified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13	Is there a clear definition of the options under evaluation?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Philips criteria		NICE-TA588	NICE-TA755	NICE-HST15-type1	NICE-HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam -2021	CADTH Onasemnogene - 2021	Meijer et al., 2023	Broekhoff et al., 2021
14	Have all feasible and practical options been evaluated?	No	No	No	No	No	No	No	No	No	No
15	Is there justification for the exclusion of feasible options?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
16	Is the chosen model type appropriate given the decision problem and specified casual relationships within the model?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
17	Is the time horizon of the model sufficient to reflect all important differences between the options?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
18	Are the time horizon of the model, the duration of treatment and the duration of treatment described and justified?	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	No	Yes
19	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

Philips criteria		NICE-TA588	NICE-TA755	NICE-HST15-type1	NICE-HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam -2021	CADTH Onasemnogene - 2021	Meijer et al., 2023	Broekhoff et al., 2021
20	Is the cycle length defined and justified in terms of the natural history of disease?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Data											
21	Are the data identification methods transparent and appropriate given the objectives of the model?	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Unclear
22	Where choices have been made between data sources are these justified appropriately?	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
23	Has particular attention been paid to identifying data for the important parameters of the model?	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
24	Has the quality of the data been assessed appropriately?	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
25	Where expert opinion has been used are the methods described and justified?	Yes	Yes	Unclear	Unclear	Yes	Yes	Unclear	Unclear	No	No
26	Is the data modelling methodology based on justifiable	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No	Unclear

Philips criteria		NICE-TA588	NICE-TA755	NICE-HST15-type1	NICE-HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam -2021	CADTH Onasemnogene - 2021	Meijer et al., 2023	Broekhoff et al., 2021
	statistical and epidemiological techniques?										
27	Is the choice of baseline data described and justified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
28	Are transition probabilities calculated appropriately?	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No	Yes
29	Has a half-cycle correction been applied to both costs and outcomes?	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Unclear
30	If not, has the omission been justified?	-	-	-	-	-	Unclear	Unclear	Unclear	-	Unclear
31	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear
32	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes

Philips criteria		NICE-TA588	NICE-TA755	NICE-HST15-type1	NICE-HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam -2021	CADTH Onasemnogene - 2021	Meijer et al., 2023	Broekhoff et al., 2021
33	Have alternative extrapolation assumptions been explored through sensitivity analysis?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
34	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
35	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis	No	No	No	No	No	No	No	No	No	Yes
36	Are the costs incorporated into the model justified?	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
37	Has the source for all costs been described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
38	Have discount rates been described and justified given the target decision maker?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
39	Are the utilities incorporated into the model appropriate?	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes

Philips criteria		NICE-TA588	NICE-TA755	NICE-HST15-type1	NICE-HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam -2021	CADTH Onasemnogene - 2021	Meijer et al., 2023	Broekhoff et al., 2021
40	Is the source of utility weights referenced?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
41	Are the methods of derivation for the utility weights justified?	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
42	Have all data incorporated into the model been described and referenced in sufficient detail?	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
43	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate?)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear
44	Is the process of data incorporation transparent?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
45	If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes
46	If data have been incorporated as distributions, is it clear that second	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes

Philips criteria		NICE-TA588	NICE-TA755	NICE-HST15-type1	NICE-HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam -2021	CADTH Onasemnogene - 2021	Meijer et al., 2023	Broekhoff et al., 2021
	order uncertainty is reflected?										
47	Have the four principal types of uncertainty been addressed?	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No
48	If not, has the omission of particular forms of uncertainty been justified?	-	-	-	-	-	No	No	No	No	No
49	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
50	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
51	Has heterogeneity been dealt with by running the model separately for different sub-groups?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
52	Are the methods of assessment of parameter uncertainty appropriate?	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes

Philips criteria		NICE-TA588	NICE-TA755	NICE-HST15-type1	NICE-HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam -2021	CADTH Onasemnogene - 2021	Meijer et al., 2023	Broekhoff et al., 2021
53	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
54	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
55	Are any counterintuitive results from the model explained and justified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
56	If the model has been calibrated against independent data, have any differences been explained and justified?	Unclear	Unclear	Unclear	-	-	-	-	-	-	-
57	Have the results been compared with those of previous models and any differences in results explained?	Yes	Yes	Yes	Yes	Unclear	No	No	No	Yes	Yes
N- No; N/A- Not Applicable; Y- Yes; UNC-Unclear											

Table 136: Critical appraisal of the economic models in the original systematic review using an adapted Philips checklist (Part II)

Philips criteria		SMC Nusinersen - 2018	SMC Onasemn ogene - 2021	SMC Risdiplam- 2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sa nchez et al. 2019	Thokala et al. 2020	NCPE- 2017
Structure											
1	Is there a clear statement of the decision problem?	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Is the objective of the model specified and consistent with the stated decision problem?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Is the primary decision maker specified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	Is the perspective of the model stated clearly?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	Are the model inputs consistent with the stated perspective?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6	Has the scope of the model been stated and justified?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
7	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unclear
9	Are the sources of the data used to develop the structure of the model specified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Philips criteria		SMC Nusinersen - 2018	SMC Onasemn ogene - 2021	SMC Risdiplam- 2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sa nchez et al. 2019	Thokala et al. 2020	NCPE- 2017
10	Are the causal relationships described by the model structure justified appropriately?	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
11	Are the structural assumptions transparent and justified?	No	No	No	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
12	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	No	No	No	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear
13	Is there a clear definition of the options under evaluation?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14	Have all feasible and practical options been evaluated?	Yes	No	No	Yes	Yes	Yes	No	Yes	No	Yes
15	Is there justification for the exclusion of feasible options?	-	Unclear	Unclear	-	-	-	Unclear	-	Unclear	-
16	Is the chosen model type appropriate given the decision problem and specified casual relationships within the model?	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
17	Is the time horizon of the model sufficient to reflect all important differences between the options?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
18	Are the time horizon of the model, the duration of	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unclear

Philips criteria		SMC Nusinersen - 2018	SMC Onasemn ogene - 2021	SMC Risdiplam- 2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sa nchez et al. 2019	Thokala et al. 2020	NCPE- 2017
	treatment and the duration of treatment described and justified?										
19	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unclear
20	Is the cycle length defined and justified in terms of the natural history of disease?	Unclear	Yes	Yes	No	Unclear	Yes	Yes	Yes	Yes	Yes
Data											
21	Are the data identification methods transparent and appropriate given the objectives of the model?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
22	Where choices have been made between data sources are these justified appropriately?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
23	Has particular attention been paid to identifying data for the important parameters of the model?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
24	Has the quality of the data been assessed appropriately?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Philips criteria		SMC Nusinersen - 2018	SMC Onasemn ogene - 2021	SMC Risdiplam- 2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sa nchez et al. 2019	Thokala et al. 2020	NCPE- 2017
25	Where expert opinion has been used are the methods described and justified?	Unclear	Unclear	Unclear	Unclear	-	-	-	Unclear	-	-
26	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
27	Is the choice of baseline data described and justified?	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear
28	Are transition probabilities calculated appropriately?	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear
29	Has a half-cycle correction been applied to both costs and outcomes?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear
30	If not, has the omission been justified?	-	-	-	-	-	-	-	-	-	-
31	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
32	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
33	Have alternative extrapolation	Unclear	Unclear	Unclear	No	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Philips criteria		SMC Nusinersen - 2018	SMC Onasemn ogene - 2021	SMC Risdiplam- 2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sa nchez et al. 2019	Thokala et al. 2020	NCPE- 2017
	assumptions been explored through sensitivity analysis?										
34	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	Yes	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes	Unclear	Unclear
35	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
36	Are the costs incorporated into the model justified?	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
37	Has the source for all costs been described?	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
38	Have discount rates been described and justified given the target decision maker?	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
39	Are the utilities incorporated into the model appropriate?	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
40	Is the source of utility weights referenced?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
41	Are the methods of derivation for the utility weights justified?	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes

Philips criteria		SMC Nusinersen - 2018	SMC Onasemn ogene - 2021	SMC Risdiplam- 2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sa nchez et al. 2019	Thokala et al. 2020	NCPE- 2017
42	Have all data incorporated into the model been described and referenced in sufficient detail?	No	No	No	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear
43	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate?)	No	No	No	Yes	No	No	No	No	No	Unclear
44	Is the process of data incorporation transparent?	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear
45	If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear
46	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
47	Have the four principal types of uncertainty been addressed?	Unclear	Unclear	Unclear	No	No	Yes	Yes	Yes	Yes	Unclear
48	If not, has the omission of particular forms of uncertainty been justified?	-	-	-	Unclear	No	-	-	-	-	Unclear
49	Have methodological uncertainties been	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Philips criteria		SMC Nusinersen - 2018	SMC Onasemn ogene - 2021	SMC Risdiplam- 2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sa nchez et al. 2019	Thokala et al. 2020	NCPE- 2017
	addressed by running alternative versions of the model with different methodological assumptions?										
50	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
51	Has heterogeneity been dealt with by running the model separately for different sub-groups?	Unclear	Unclear	Unclear	No	No	No	No	Yes	No	Unclear
52	Are the methods of assessment of parameter uncertainty appropriate?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unclear
53	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Unclear	Unclear	Unclear	Unclear	No	No	Yes	Yes	Yes	Unclear
54	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
55	Are any counterintuitive results from the model explained and justified?	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No
56	If the model has been calibrated against independent data, have any differences been explained and justified?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Philips criteria		SMC Nusinersen - 2018	SMC Onasemn ogene - 2021	SMC Risdiplam- 2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sa nchez et al. 2019	Thokala et al. 2020	NCPE- 2017
57	Have the results been compared with those of previous models and any differences in results explained?	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No
N- No; N/A- Not Applicable; Y- Yes; UNC-Unclear											

Table 137: Critical appraisal of the economic model included in the systematic review update using an adapted Philips checklist

Structure		Khuntha et al. 2024
1	Is there a clear statement of the decision problem?	Yes
2	Is the objective of the model specified and consistent with the stated decision problem?	Yes
3	Is the primary decision maker specified?	Yes
4	Is the perspective of the model stated clearly?	Yes
5	Are the model inputs consistent with the stated perspective?	Yes
6	Has the scope of the model been stated and justified?	Yes
7	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Yes
8	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Yes
9	Are the sources of the data used to develop the structure of the model specified?	Yes
10	Are the causal relationships described by the model structure justified appropriately?	Yes

11	Are the structural assumptions transparent and justified?	Yes
12	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Yes
13	Is there a clear definition of the options under evaluation?	Yes
14	Have all feasible and practical options been evaluated?	Yes
15	Is there justification for the exclusion of feasible options?	Yes
16	Is the chosen model type appropriate given the decision problem and specified casual relationships within the model?	Yes
17	Is the time horizon of the model sufficient to reflect all important differences between the options?	Yes
18	Are the time horizon of the model, the duration of treatment and the duration of treatment described and justified?	Yes
19	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Yes
20	Is the cycle length defined and justified in terms of the natural history of disease?	Yes
Data		
21	Are the data identification methods transparent and appropriate given the objectives of the model?	Unclear
22	Where choices have been made between data sources are these justified appropriately?	Yes
23	Has particular attention been paid to identifying data for the important parameters of the model?	Yes
24	Has the quality of the data been assessed appropriately?	Unclear
25	Where expert opinion has been used are the methods described and justified?	Yes
26	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	Yes
27	Is the choice of baseline data described and justified?	Yes
28	Are transition probabilities calculated appropriately?	Yes
29	Has a half-cycle correction been applied to both costs and outcomes?	Unclear

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30	If not, has the omission been justified?	Unclear
31	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	Yes
32	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	Yes
33	Have alternative extrapolation assumptions been explored through sensitivity analysis?	Unclear
34	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	NA
35	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis	NA
36	Are the costs incorporated into the model justified?	Yes
37	Has the source for all costs been described?	Yes
38	Have discount rates been described and justified given the target decision maker?	Yes
39	Are the utilities incorporated into the model appropriate?	Yes
40	Is the source of utility weights referenced?	Yes
41	Are the methods of derivation for the utility weights justified?	Yes
42	Have all data incorporated into the model been described and referenced in sufficient detail?	Yes
43	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate?)	No
44	Is the process of data incorporation transparent?	Yes
45	If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?	Yes
46	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	Yes
47	Have the four principal types of uncertainty been addressed?	Yes
48	If not, has the omission of particular forms of uncertainty been justified?	NA
49	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	Yes

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50	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	Yes
51	Has heterogeneity been dealt with by running the model separately for different sub-groups?	No
52	Are the methods of assessment of parameter uncertainty appropriate?	Yes
53	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	NA
54	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	Yes
55	Are any counterintuitive results from the model explained and justified?	Yes
56	If the model has been calibrated against independent data, have any differences been explained and justified?	Unclear
57	Have the results been compared with those of previous models and any differences in results explained?	Yes
N/A- Not Applicable		