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Review of economic modelling evidence of NICE appraisals of rare disease treatments for spinal muscular atrophy

Lea Wiedmann[a,*] and John Cairns[b]

[a] *Department of Health Services Research and Policy; Faculty of Public Health and Policy; London School of Hygiene and Tropical Medicine. Address: 15-17 Tavistock Place London WC1H 9SH (UK). Email: Lea.Wiedmann@lshtm.ac.uk. ORCiD: https://orcid.org/0000-0002-8259-0774*

[b] *Department of Health Services Research and Policy; Faculty of Public Health and Policy; London School of Hygiene and Tropical Medicine. Address: 15-17 Tavistock Place London WC1H 9SH (UK). ORCiD: https://orcid.org/0000-0001-6442-0440*

*Corresponding author

Abstract

Introduction: The National Institute of Health and Care Excellence (NICE) in England has appraised three treatments for spinal muscular atrophy (SMA), namely, nusinersen, onasemnogene abeparvovec, and risdiplam. As rare disease treatments (RDTs) commonly face challenges in health technology assessment (HTA) processes due to their clinical and economic uncertainties, an in-depth review of these appraisals is useful to enable a deeper understanding of economic modelling considerations for SMA.

Areas covered: This review is a detailed analysis of NICE appraisals for SMA and aims to compare the economic modelling evidence of the three RDTs. This is done by examining differences and similarities and by discussing critical outstanding issues across the economic evaluations of the appraisals.

Expert opinion: This article aims to contribute to the development of evidence that can be used as guidance to inform resource allocation decisions for RDTs for SMA, but also to be a resource about approaches for the generation, analysis and interpretation of economic modelling evidence for RDTs more broadly.

Key words: health technology assessment, National Institute of Health and Care Excellence, nusinersen, onasemnogene abeparvovec, risdiplam, spinal muscular atrophy

Article highlights:

- Currently, three disease-modifying treatments for spinal muscular atrophy have been appraised by NICE and are available to patients in England
- The comparative assessment of economic evaluations examining the benefits and costs of these treatments for SMA reflect six critical outstanding issues, relating to the classification of SMA health states, long-term survival, the collection and quantification of resource use

data, patient utility values, caregiver utility values, and additional utility values for patients on treatment compared to best supportive care (BSC)

- A consensus on how these issues should be approached in economic evaluations for SMA is desirable to achieve more consistency across appraisals

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1. Introduction

Health Technology Assessment (HTA) has been used to evaluate the properties and effects of health technologies and to establish their value in terms of benefits, risks and costs [1, 2]. In England, HTAs are conducted by the National Institute for Health and Care Excellence (NICE) to inform resource allocation decisions in the healthcare system. Treatments for rare diseases (RDTs) are also appraised by NICE but in contrast to treatments for diseases which are more prevalent, RDTs pose significant challenges to HTA processes [3]. This is because they are typically associated with clinical and economic uncertainties [3], which complicate judgements about their benefits in comparison to other alternatives. At the same time, there is no approved treatment for the vast majority (95%) of rare diseases, leaving a large unmet medical need [4].

In this context, NICE appraisals for spinal muscular atrophy (SMA) are a relevant case study for analysis. SMA is a severe neuromuscular disease which affects motor neurons in the spinal cord [5]. The disease is caused by deletion, conversion or mutation of the survival motor neuron (SMN) 1 gene which limits expression of the SMN protein [6]. The resulting degeneration of motor neurons leads to progressive muscle weakness, paralysis and death, with SMA being the leading genetic cause of death in infancy [6]. Nusinersen, onasemnogene abeparvovec and risdiplam were appraised by NICE following their approval by the European Medicines Agency (EMA). Much information is available for SMA from the three NICE appraisals, compared with the vast majority of rare diseases where no authorized treatments exist. This merits a detailed, comparative assessment of these appraisals. Moreover, all three RDTs for SMA are very expensive in terms of costs per treatment for healthcare systems. Thus, resource allocation decisions for RDTs have to consider willingness-to-pay for extremely expensive treatments that benefit only a small number of patients [7, 8]. Lastly, SMA displays important characteristics which are also present in other rare diseases, including genetic origin, childhood-onset, a chronically debilitating and life-threatening nature, unmet need [9], and high cost-effectiveness ratios of their treatments which generally results in failing standard cost-effectiveness criteria [8, 10].

To the best of the authors' knowledge, this is the first detailed analysis of the economic modelling evidence of the three NICE SMA appraisals. Thus, by comparatively analyzing the appraisals with a focus on the economic model, survival modelling, cost and healthcare resource use, the measurement and valuation of health effects, and the committee recommendation, this review aims to enable a deeper understanding of economic modelling considerations for SMA. This is done by examining differences and similarities, and by discussing critical outstanding issues across the economic evaluations of the three appraisals.

2. Economic uncertainties

Economic uncertainties in the evidence base of RDTs often relate to economic modelling considerations regarding cost and health benefit. Often, only limited information about the direct and indirect costs of rare diseases is available [11], which complicates quantifying resource use. For SMA it has been demonstrated that only limited evidence for the cost of illness exist and that costs across settings and disease phenotypes are variable [12, 13]. Moreover, prices of RDTs are typically high because 1) manufacturers must recoup their incurred costs from a limited number of patients which results in high per-patient acquisition costs [8], 2) RDTs often cover conditions where unmet need is usually high and so they are considered to have high value [14], and 3) some RDTs represent innovative breakthrough therapies, for example gene therapies, and thus promise major, potentially life-long clinical benefits [15]. These considerations are also likely to be reflected in the high prices of the three RDTs for SMA; for example, the UK list price for onasemnogene abeparvovec was given at £1.79 million per injection upon approval, and as such, this RDT was labelled as the most expensive

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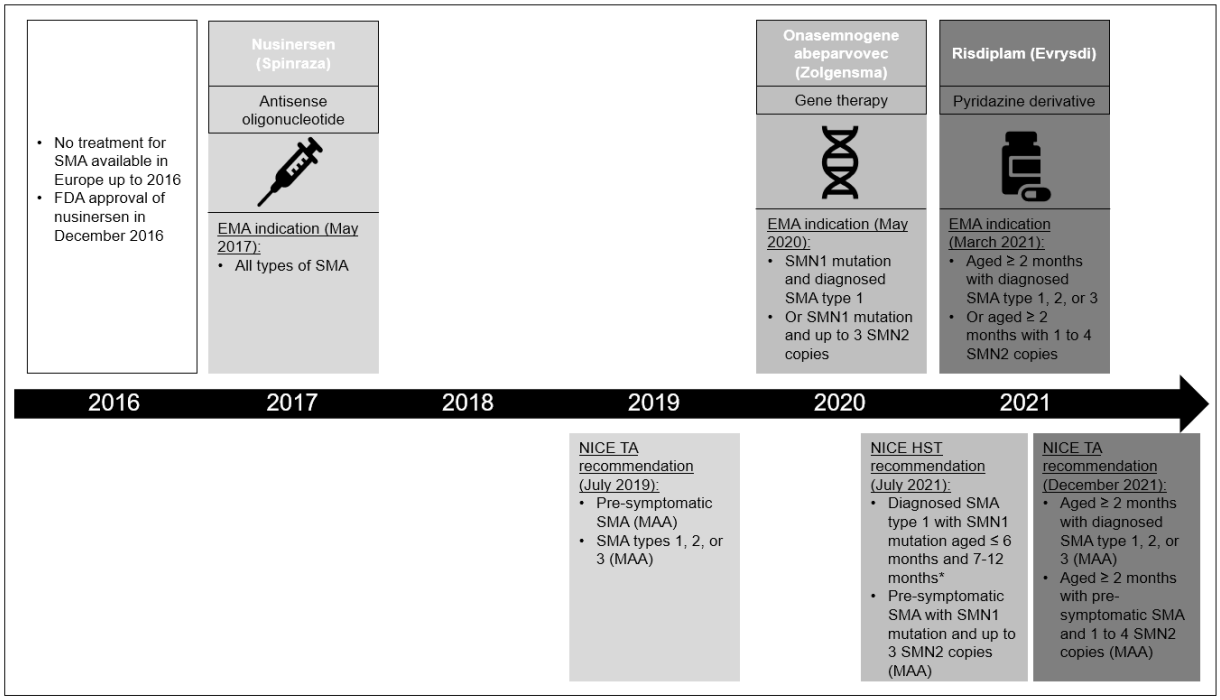
pharmaceutical worldwide at that time [16]. Further, due to the myriad of challenges associated with the use and development of patient-reported outcome measures (PROMs) for rare diseases in HTA [17], generating robust health state utility values to inform economic models is often difficult. There is also no agreement on the most appropriate means by which to estimate utility values [18]. Similarly, it has been argued that for SMA robust utility data are absent and that the available utility data often fail to meet reference cases of HTA bodies [19]. Lastly, modelling survival for rare disease patients on new treatments is often associated with uncertainty, including for SMA [20], and primarily due to small sample sizes and limited long-term follow-up of patients.

3. Available Treatments for SMA

Nusinersen was the first treatment for SMA, approved by the EMA in May 2017 [21], and recommended by NICE in single technology appraisal (STA) guidance in July 2019 [22]. It is an antisense oligonucleotide that targets the SMN2 gene so that it produces higher levels of functional SMN proteins [23]. It is administered by intrathecal injection which mainly limits its effect on central nervous system (CNS) tissue [23]. Onasemnogene abeparvovec is a gene therapy, approved by the EMA in May 2020 [24], and recommended by NICE in highly specialised technology (HST) guidance in July 2021 [25]. An adeno-associated virus (AAV) serotype 9 vector is used to induce a copy of the SMN1 gene into motor neurons which supplements them with SMN protein [26]. It is administered by a one-time, intravenous infusion resulting in a systemic expression of SMN protein [23]. Risdiplam is a small molecule and the most recently authorized treatment for SMA, approved by the EMA in March 2021 [27], and recommended by NICE in STA guidance in December 2021 [28]. Risdiplam and nusinersen both function as splicing modifiers which ultimately leads to a higher amount of functional SMN protein created by the SMN2 gene [29]. One key difference between nusinersen and risdiplam is the oral administration of the latter which enables the treatment to affect SMN levels in other systemic tissues beyond the motor neurons in the CNS [26]. Figure 1 shows the EMA-approved indication and the subsequent NICE recommendation for the three RDTs.

Figure 1. Available treatments for SMA



*Provided that permanent ventilation for more than 16 hours per day or tracheostomy is not needed. For babies aged 7 to 12 months, their treatment must be agreed by the national multidisciplinary team; onasemnogene abeparvovec is only allocated to babies who have at least a 70% chance of being able to sit independently following treatment.

Abbreviations: EMA = European Medicines Agency (EMA); FDA = US Food and Drug Administration; HST = highly specialized technology appraisal guidance; MMA = managed access agreement; SMA = spinal muscular atrophy; SMN1/2 = survival motor neuron 1/2; STA = Single Technology appraisal guidance

Figure adapted from slides shown during the ISPOR webinar "Delivering Evidence-Based Access in Rare Diseases: The Challenges in SMA" held on 05/04/2022 [30] .

Sources: [21, 24, 27, 31-33]

4. Methods

The documents available of the three NICE appraisals for the RDTs for SMA were reviewed. Relevant documents for each appraisal include the final scope, committee papers, including company evidence submissions and reports by the External Assessment Group (EAG), the final appraisal or evaluation document, and documents relating to respective managed access agreements. All documents are publicly available and were retrieved from the NICE website.

Data for different aspects of the cost-effectiveness evidence were extracted from the respective HTA reports. Data extraction was based on NICE's evidence submission templates for manufacturers and reports by the EAG, and it focused primarily on aspects that were discussed by NICE in the final appraisal or evaluation document of the respective RDTs. Therefore, data was extracted for four categories: 1) the economic model, 2) survival modelling, 3) cost and healthcare resource use, 4) measurement and valuation of health effects, and 5) the committee recommendation. For each category, data sources, assumptions by the manufacturer, and comments by the appraisal committee and the EAG were extracted. Data was extracted by a single person (LW) which may be a potential limitation.

5. Results

5.1 Economic models

For all RDTs Markov models were submitted to NICE modelling costs and health benefits over a lifetime horizon. For all three RDTs, model health states were based on motor function milestones measured by a range of assessment scales to evaluate different types of SMA. All models were updated several times throughout the appraisal process. Table 1 summarizes the main aspects of the economic analysis for each RDT.

Table 1. Overview of economic analyses for type 1 and type 2/3 SMA patients

	Nusinersen (TA588)	**Onasemnogene abeparvovec (HST15)**	**Risdiplam (TA755)**
Model type and patient population	2 Markov models : - Infantile-onset (type 1 SMA) - Later-onset (type 2/3 SMA)	1 Markov model : - Infantile-onset (type 1 SMA), including two scenario analyses for pre-symptomatic patients	2 Markov models: - Infantile-onset (type 1 SMA) - Later-onset (type 2/3 SMA)
Time horizon	Type 1: 60 years (lifetime) Type 2/3: 80 years (lifetime)	Short-term: 3 years Long-term: lifetime	90 years (lifetime)

Comparator	RWC (similar to BSC)	BSC	BSC
Perspective	Payer (UK NHS and PSS)	Payer (UK NHS and PSS)	Payer (UK NHS and PSS)
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 and15 months, and every 4 months thereafter	- Short-term: 6 months - Long-term: 1 year	1 month
Discount rate	3.5% (costs and benefits)	3.5% (costs and benefits)	3.5% (costs and benefits)
Health benefits	LYG, QALYs	LYG, QALYs	LYG, QALYs
Model structure	- Type 1: 8 states based on HINE-2; plateau at 54 and 66 months - Type 2/3: 7 states based on HMFSE and WHO criteria; plateau at 15 and 27 months - Patients represent either improvers on treatment, plateauers on treatment, or worseners who discontinued treatment <u>Stopping rule</u> - Patients stop treatment when a) no milestones are achieved by end of month 13 (type 1) or month 15 (type 2/3), (b) they cannot receive nusinersen following scoliosis surgery, or (c) they become worseners	- Type 1: 6 states based on achieved motor function milestones; model framework broadly aligned with the model structure for type 1 and pre-symptomatic SMA patients used in the ICER report - 2 scenario analyses for pre-symptomatic patients based on the type 1 model - Short-term model (up to 3 years) and long-term model extrapolating study data	- Type 1: 6 states based on HINE-2; plateau at 66 months - Type 2/3: 6 states based on MFM-32 and HMFSE; plateau at 26 months <u>Stopping rule</u> - Restriction of risdiplam use to a maximum of 50 years (type 1) and 30 years (type 2/3) - After the treatment plateau, patients in the non-sitting and permanent ventilation states stop treatment with no effect on OS, utility values or transition probabilities (type 1), and patients in the non-sitting and sitting supported states stop treatment with a linear loss of motor milestones so that transition probabilities equal those for BSC after 120 months, but with no effect on OS and utility values (type 2/3)

Abbreviations: BSC = best supportive care; HFMSE= Hammersmith Functional Motor Scale Expanded; HINE-2 = Hammersmith Infant Neurological Examination Modul 2; LYG = life-year gained; MFM-32 = Motor Function Measure; NHS = National Health Service; OS = overall survival; PSS = Personal Social Services; QALY = quality-adjusted life year; RWC = real world care; SMA = spinal muscular atrophy; ICER = Institute for Clinical and Economic Review; WHO = World Health Organization

All models employed different structural assumptions. The model structure for nusinersen was very complex which hindered a thorough understanding [34], and the nusinersen and risdiplam models were limited by the inability to reflect appropriate stopping rules accurately [34, 35]. Particularly for risdiplam the committee did not accept the assumption of continued benefits, including no change in overall survival (OS) and additional on-treatment benefits, after stopping therapy [35]. Overall, the limitations in the model structure contributed to increased uncertainty of cost-effectiveness results (nusinersen) [34], and led to the requirement for an updated model structure for the guidance

review (risdiplam) [35]. Further, the conclusions by the committee regarding the model structure of the onasemnogene abeparvovec models highlighted that the modelling for the pre-symptomatic population was not appropriate because the manufacturer erroneously assumed that all pre-symptomatic patients would develop type 1 SMA [36].

For all three models, it was noted that it was likely that there were benefits not captured by the models [34-36]. References were made to other factors that also affect health-related quality of life (HRQoL), including participating in activities, respiratory function, pain, physical impairment, and the benefits of gaining specific motor skills such as independence, the ability to self-care, learning to write, or going to school (nusinersen) [34], interim motor milestones, speech and non-verbal communication, reduced fatigue, increased stamina, better respiratory function, ability to swallow and fine motor skills (onasemnogene abeparvovec) [36, 37], and fine motor skills, including upper limb function, and respiratory and bulbar function such as the ability to swallow, speak and communicate (risdiplam) [35]. However, despite these limitations, all RDTs were recommended by the committee (see section 5.5).

5.2 Survival modelling

While clinical data demonstrated improvements in survival and motor function of SMA patients for all three RDTs [37-39], long-term survival outcomes remained a key area of uncertainty [34-36]. Table 2 gives an overview of key assumptions for modelled survival for the three RDTs.

Table 2. Assumptions for survival modelling (final models)

	Nusinersen (TA588)	Onasemnogene abeparvovec (HST15)	Risdiplam (TA755)
Type 1 SMA	- Weibull models fitted to trial data separately to each treatment group - Assumption of proportional hazards, but HR tapered over 120 months (type 1) - Mortality adjustment factor of 0.75 applied in better health states (sitting, standing, walking)	- Permanent assisted ventilation: Exponential model fitted to Gregoretti et al. [81] - Not sitting: Weibull model fitted to natural history study (NeuroNext) - Sitting: Generalized gamma model fitted to Zerres et al. [82]; assuming the same life expectancy as type 2 patients - Walking & within a broad range of normal development: General population mortality (ONS lifetables); assuming the same life expectancy as type 3 patients	- MAIC due to single-arm trial (FIREFISH) - Permanent assisted ventilation, not sitting, sitting (risdiplam group): Exponential model fitted to trial data - Not sitting (BSC group): Application of inverse HR derived from indirect comparison - Permanent assisted ventilation, sitting (BSC group): Same as risdiplam group - Standing & walking: Based on type 2 Gompertz distribution applied in type 2/3 model
Type 2/3 SMA	- Flexible spline model (2-knots) - Mortality adjustment factor of 0.75 applied in better health states (standing, walking)	N/A	- Not sitting, sitting supported, sitting unsupported (BSC group): Gompertz model fitted to IPD from six natural history studies; weighted survival model assuming general population mortality for type 3 patients and a worse survival prognosis for type 2 patients - Not sitting, sitting supported, sitting unsupported (risdiplam group): same as control group, except a mortality adjustment factor of 0.75 for type 2 patients (based on TA588)

			- Standing & walking: General population mortality (ONS life tables)

Abbreviations: BSC = best supportive care; HR = hazard ratio; IPD = individual patient data; MAIC = matched-adjusted indirect comparison; ONS = Office of National Statistics

The modelling of survival proved challenging in all three appraisals, primarily owing to a lack of data. In the nusinersen and risdiplam appraisals the modelling included a mortality adjustment, whereby those attaining better health states (such as, sitting and walking) were assigned a weighted survival probability, 75% based on the mortality risk of type 2/3 SMA patients and 25% based on a higher mortality risk observed in type 1 SMA patients in the ENDEAR and SHINE trials [38, 40]. The 0.75 adjustment factor was based on clinical opinion which suggested a range from 0.5 to 1.0, again highlighting the great uncertainty [41]. No mortality adjustment factor was applied in the case of onasemnogene abeparvovec, but in a broadly similar fashion patients reaching the sitting and walking health states were assumed to have the same life expectancy as type 2 and 3 SMA patients respectively [37]. The latter being assumed to be the same life expectancy as the general public [37].

The final models in both the nusinersen and risdiplam appraisals also assumed that a proportion of patients 'plateau', that is, they no longer further improve although they continue to receive treatment [40, 42]. While accepting that this is clinically plausible, the committee considered this to be a further source of uncertainty, because there was no robust data by which to determine the timing of the plateau, nor whether a patient's condition worsens after the plateau [34]. Further comments by the EAG and the committee related to survival modelling can be found in the online supplementary material.

5.3 Cost and healthcare resource use

For the nusinersen models, the manufacturer conducted a real-world-evidence (RWE) survey among pediatric neurological consultants in 9 UK centers to estimate cost per SMA type [40]. However, health state costs in the final nusinersen models were based on data from two centers only due to concerns about the representativeness of the data collected in other centers [43]. Also, total care costs might have been underestimated [34]. For the risdiplam models, the manufacturer conducted a UK Burden of Illness study to collect cost data from SMA patients and their caregivers through online surveys [38]. However, resulting healthcare costs were lower than those used in the final nusinersen models and thus cost data from the RWE survey were used for modelling [38]. In addition, permanent ventilation costs in the type 1 model were increased [38] and costs for SMA complications were added [44]. The EAG questioned the appropriateness of these assumptions and noted that assuming additional costs was not in line with the assumptions in TA588 [45, 46]. To estimate health state costs to inform the onasemnogene abeparvovec model, the manufacturer conducted a UK healthcare resource utilization (UK HCRU) study with 16 UK clinical experts [37]. The approach to convert estimates into cost categories for the model was considered complex by the EAG, also noting that the manufacturer could have designed cost categories at the forefront of the study [47]. As such, the EAG proposed the SHELF methodology as an alternative study design in which clinical experts agree on a consensus about the true value of each cost category to prevent having substantial outliers [47]. Furthermore, the EAG noted a substantial difference between cost estimates used by the manufacturer and those used in a report of the US Institute for Clinical and Economic Review (US ICER) which reviewed the clinical evidence and cost-effectiveness of nusinersen and onasemnogene abeparvovec [47]. However, as these differences were assumed to be due to differences in setting and perspective (US vs UK NHS), the EAG agreed with the manufacturer to not use the estimates by the US ICER [47]. None of the models explicitly included age-dependent health

state costs. Table 3 gives an overview of the sources and assumptions of the health state costs for the three RDTs.

Table 3. Overview of cost and healthcare resource use for type 1 and type 2/3 SMA patients

	Nusinersen (TA588)	Onasemnogene abeparvovec (HST15)	Risdiplam (TA755)
Sources and assumptions of health state cost in the final models	- Health state resource use sourced from the 2017 RWE survey - Only values from two centers included due to concerns about representativeness of data collected in other centers - Type 1 SMA costs doubled following advice from manufacturer's experts	- Health state resource use sourced from the UK HCRU study - Ventilatory support costs sourced from Noyes et al. [83] - Type of ventilatory support and proportion of patients receiving it sourced from manufacturer's UK clinical advisory board and Gregoretti et al. [81] - Costs account for SMA complications, including scoliosis surgery - Resource use in the sitting and walking state assumed to be equal to resource use for patients with type 2 and 3 SMA respectively	- Health state resource use source as for nusinersen - Cost of permanent ventilation health state assumed to be 175% times the not sitting health state - Additional costs associated with SMA complications applied to all patients in the BSC arm, and to 50% of patients in the risdiplam arm in the two worst health states in type 1 and 2/3 models - Unit costs and frequencies of each complication were taken from NHS Reference Costs 2019/20 and the Roche Burden of Illness study - Proportion of patients affected by SMA complications was based on assumptions

Abbreviations: BSC = best supportive care; HCRU = healthcare resource utilization; NHS = National Health Service; RWE = real-world evidence; SMA = spinal muscular atrophy

5.4 Measurement and valuation of health effects

For type 1 patients, no HRQoL data was collected in clinical trials across appraisals. For type 2/3 patients, PedsQL data was collected in the CHERISH trial (nusinersen) and mapped to the EQ-5D-3L using a published algorithm by Khan et al. [48], and EQ-5D-5L was collected in the SUNFISH trial (risdiplam) and mapped to the EQ-5D-3L format [38]. However, due to limited face validity, these mapped utility values were only included in the original models for nusinersen and were excluded a priori by the manufacturer from the risdiplam models [38, 49]. In addition, data on functional-related independence and upper limb ability in type 2/3 patients was collected in the SUNFISH trial using the SMA Independence Scale (SMAIS) and the results served as exploratory outcomes [38]. All economic models excluded adverse events due to treatment [37-39], but models accounted for complications, including scoliosis, associated with SMA as a disease [37, 40, 44].

In each iteration of the nusinersen models different utility values were used. This included utility values obtained by mapping PedsQL data from CHERISH to EQ-5D-3L, utility values from Lloyd et al. [50], a vignette study based on clinician-proxy EQ-5D assessments, and non-preference based utility values estimated by Biogen's clinical experts in the original [39], the post-ACD [51], and the current models [40] respectively. The values of Biogen's clinical experts represent mid-points between the estimates provided by the EAG's clinical advisors and Lloyd et al. [50] and were considered more

appropriate by clinical experts [40]. The EAG considered it appropriate to use estimates derived from clinical experts due to the limited face validity of existing preference-based utility estimates [41]. Caregiver utility values were defined on a range between the average utility from Spanish caregivers in López-Bastida et al. [52] and the EQ-5D score for the general population of the UK [51]; they were implemented as disutilities being dependent on patient health status, assuming a smaller caregiver disutility in better patient health states. The EAG and the committee noted that the inclusion of caregivers increased the incremental cost-effectiveness ratio (ICER) in the type 1 model and decreased the ICER in the type 2/3 model [34]. These ICERs were counterintuitive as they suggested that it would be more cost-effective to treat type 2/3 SMA than type 1 SMA [34]. Thus, a life-extending treatment, particularly for type 1 SMA, seemed to be less cost-effective [34]. Lastly, the nusinersen models did not apply additional utility values for patients on treatment compared to the control group. Overall, the committee concluded that utility values in the nusinersen models were uncertain and might have not captured all benefits related to gaining specific motor function skills [34].

For the onasemnogene abeparvovec models, a mix of preference-based and non-preference-based utility values was chosen [37]. The utility values generated by Novartis' de novo UK utilities study, in which 100 UK adults from the general population valued four health state vignettes representing the model health states, were not used in the model because they resulted in negative QALYs which was considered to lack face validity [53]. Despite the uncertainty around the chosen utility values, the committee accepted them for decision-making [36]. In contrast to the risdiplam and nusinersen models, the onasemnogene abeparvovec models did not include caregiver utility values [37]. The EAG tested the inclusion of caregiver disutility in a scenario analysis for the onasemnogene abeparvovec appraisal and noted that this increased the ICER substantially [36, 47]. Lastly, the model applied additional utility values for patients on treatment compared to BSC to capture interim motor milestones within health states [37]. This was based on the US ICER report and following EAG preferences [37]. The committee accepted the additional on-treatment utility values as benefits not captured in the model health states were demonstrated in the clinical studies [36].

In the original risdiplam models, non-preference-based utility values from the EAG's clinical experts in TA588 and values from Lloyd et al. [54] were used for the type 1 and type 2/3 population respectively [38]. The EAG noted that the available preference-based and non-preference-based utility values tended to lack face validity and scientific rigor respectively [46]. The EAG also commented that it was inconsistent to use preference-based utility values for one SMA population (type 2/3) and non-preference-based values for the other (type 1) [46]. Eventually, the EAG asserted that the utility values obtained from the manufacturer's clinical experts used in TA588 represented the most appropriate source for patient utility values and the manufacturer subsequently updated the type 1 and type 2/3 models accordingly [46, 55]. To account for caregiver utility, the original risdiplam models adopted an additive approach in which caregiver HRQoL increased with patient motor milestone achievement [38]. The EAG did not accept this approach as it assumed that HRQoL of caregivers was zero after patient death with the implication that bereavement of caregivers was not considered [46, 55]. Eventually, the final risdiplam models adopted the EAG's disutility approach for type 2/3 patients and an amended disutility approach for type 1 patients [44, 45, 55]. The committee considered that the EAG's disutility approach increased the ICER in the type 1 model substantially [35], suggesting counterintuitive results with a similar effect as in the nusinersen models. The EAG did not accept the manufacturer's amended disutility approach for type 1 patients, also because it was inconsistent to assume that caregivers are affected only up to a specific timepoint (10.2 years) but not beyond [35, 45]. The committee noted the limitations of these approaches and concluded that the amended disutility approach for type 1 patients was not appropriate [35].

Lastly, to account for the benefits of risdiplam in fine motor skills, including upper limb function, additional utility values for patients on treatment compared to BSC were added after technical engagement [42] and increased after consultation [45]. The EAG did not support the proposed additional utility values as they were based on assumptions, and there was uncertainty around the number of patients receiving risdiplam that incure these utility gains and around the duration thereof [35]. Moreover, the manufacturer added disutilities due to SMA complications to all patients receiving BSC and to 50% of patients receiving risdiplam in specific health states [44]. The EAG noted that this approach was limited due to possible double-counting and implausible clinical assumptions and net utility values [35]. While the committee was sympathetic to the argument that some benefits might not have been captured in the economic modelling, it concluded that the approach to account for additional benefits of risdiplam from fine motor skills and fewer complications was not appropriate due to the resulting implausible utility values [35]. Eventually, the committee highlighted its preference for an elicitation approach, similar to the approach used in TA588, to generate more robust utility values [35]. Table 4 summarizes the sources and assumptions of the measurement and valuation of health effects in the three appraisals.

Table 4. Overview of the measurement and valuation of health effects for type 1 and type 2/3 SMA patients

	Nusinersen (TA588)	**Onasemnogene abeparvovec (HST15)**	**Risdiplam (TA755)**
HRQoL data from clinical trials	- PedsQL data from CHERISH trial (type 2/3 SMA) - Mapped to the EQ-5D-3L format using a published algorithm by Khan et al. [44] - Mapped values were adapted for the original type 1 model based on an assumed correspondence of health states between the type 1 and 2/3 models	N/A	- EQ-5D-5L data from SUNFISH trial (type 2/3) - Mapped to the EQ-5D-3L format - SMA Independence Scale (SMAIS) data for patients and caregivers from SUNFISH
Sources and assumptions of utility values used in the final models	<u>Patients (type 1 and type 2/3 SMA)</u> - Utility values estimated by manufacturer's clinical experts <u>Caregiver (type 1 and type 2/3 SMA)</u> - Implemented as disutilities; based on a range defined by the average utility from Spanish caregivers in López-Bastida et al. [48] and the EQ-5D score for the general population of the UK - Assumed 3 caregivers per patient (type 1)	<u>Patients</u> - Permanent assisted ventilation: Assumption based on the EAG interim report - Not sitting: Parent-proxy EQ-5D value based on Thompson et al. [84] - Sitting: Estimate from EAG's clinical experts in TA588 - Walking & within a broad range of normal development: General population utility based on Ara and Brazier [85]	<u>Patients</u> - Utility values as for nusinersen <u>Caregiver (type 1)</u> - Application of an amended disutility approach which assumed a disutility applied for BSC and risdiplam patients until 10.23 years (mean OS BSC group), no QALY losses after 10.23 years, and a bereavement disutility of -0.04 based on Song et al. [86] from point of mean OS in both treatment arms (30.58 years for risdiplam arm)

	- Assumed 2 caregivers per patient, with 3 caregivers for patients unable to sit (type 2/3)		- Assumed 2.2 caregivers per patient Caregiver (type 2/3) - Application of the ERG's disutility approach which assumed a caregiver disutility linked to patient health states. After patient death, caregiver utility returned to general population utility. Scenario 1 and 2 applied a disutility of -0.04 from Song et al. [86] for 20 years and 90 years after patient death respectively. - Assumed 2.2 caregivers per patient
Sources and assumption of additional utility values for patients on treatment compared to BSC	N/A	Patients - Additional utility values for patients on treatment compared to BSC were added to capture improvements in interim (motor) milestones within health states, including head control, rolling, crawling, standing, improvements in talking and non-verbal communication, fine motor control and learning - Utility gains of 0.1 (not sitting state) and 0.05 (sitting state) were applied based on the US ICER report	After technical engagement: - Additional utility values for patients on treatment compared to BSC were added to reflect benefits of risdiplam in fine motor skills, including upper limb function - Utility gains of 0.05 (non-sitting state) and 0.1 (sitting state) were applied based Thokala et al. [87] After consultation: - Utility values increased by 0.2 for patients and by 0.05 for caregivers in sitting and non-sitting states following feedback from patients and clinicians - To account for the uncaptured benefits of risdiplam, additional disutilities due to SMA complications of respiratory support (-0.07 from SUNFISH), severe scoliosis (-0.09 from SUNFISH) and bulbar dysfunction (-0.17 from Lloyd et al. [50]) were applied - Assumption that complications apply to all patients in the BSC arm and to 50% of patients in the risdiplam arm in the two worst health states in type 1 and 2/3 models

Abbreviations: BSC = best supportive care; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; N/A = not applicable; OS = overall survival; QALY = quality-adjusted life year; SMA = spinal muscular atrophy

5.5 Cost-effectiveness estimates and committee recommendations

All cost-effectiveness analysis (CEA) estimates that were available from the manufacturers were associated with uncertainty. For nusinersen and risdiplam, the CEA estimates were above the range of what NICE usually considers a cost-effective use of NHS resources [34, 35]. Moreover, the committee mentioned that nusinersen and risdiplam posed a financial risk to the NHS, but that the commercial agreement sufficiently managed this risk [34, 35]. Additionally, in both appraisals the committee was confident that the end-of-life (EoL) criteria were fulfilled for type 1 SMA: life expectancy for patients without treatment was less than two years and both RDTs extended life by three or more months [34, 35]. Meeting the EoL criteria allowed treatments priced above the standard NICE cost-effectiveness threshold (£20 000 - £30 000 per QALY) to be recommended up to a £50 000 per QALY threshold. This is important because aside from SMA, only advanced oncology treatments have ever met these criteria [56].

For nusinersen, treatment was recommended for all populations with a managed access agreement (MAA) [34]. However, there were substantial differences in the CEA estimates, with higher ICERs for type 1 and lower ICERs for type 2/3 patients [34]. In addition, the modification of parameters, such as assuming higher resource costs or including caregiver utility, increased the inconsistency between the ICERs for the two models [34]. Such counterintuitive ICERs were also an issue in the EAG's disutility approach for caregivers proposed in the risdiplam appraisal and in the EAG's scenario analysis including caregiver disutility in the onasemnogene abeparvovec appraisal [35, 47]. For risdiplam, the committee concluded that when its preferred model assumptions were implemented, plausible CEA estimates were likely to be higher than £50,000 per QALY gained [35]. However, despite the high CEA estimates, risdiplam was recommended for all populations with a MAA [35].

For onasemnogene abeparvovec, the committee considered the undiscounted QALY gain of 18.62 as the most plausible scenario but agreed to a lower QALY weight than 1.86 due to uncertainties in the modelling and limited evidence for long-term effectiveness [36]. Moreover, the committee agreed to reduce the discount rate for benefits and costs from 3.5% to 1.5%, despite noting that in this case, the uncertainties around costs and long-term outcomes would have a greater impact on the ICER [36]. Further, the committee confirmed that a 1.5% discount rate may be applied when treatments were associated with very high up-front costs, but benefits of the treatment likely accrued over the long-term potentially restoring patients to normal or near-full health [36]. In contrast to the two other RDTs, the committee also acknowledged the high cost of onasemnogene abeparvovec but concluded that with the manufacturer's confidential discount, the CEA estimates were likely to be within the acceptable range for a highly specialised technology [36]. Eventually, treatment for type 1 SMA patients was recommended without an MAA but the committee noted that a key limitation of the evidence base was that it included only babies younger than 6 months [36]. For the pre-symptomatic population, the committee concluded that due to the flawed assumption that all pre-symptomatic patients develop type 1 SMA, CEA estimates were not robust enough, uncertain, and likely underestimated the ICER [36]. Nonetheless, onasemnogene abeparvovec was recommended for the pre-symptomatic population with an MAA [36]. Table 5 gives an overview of the committee recommendations for the three RDTs.

Table 5. Overview of the committee recommendations

	Availability of CEA estimates per SMA population	**Fulfillment of EoL criteria per SMA population**	**Recommendation and MAA per SMA population**
Nusinersen (TA588)	✓ type 1 ✓ type 2/3 ✕ pre-symptomatic	✓ ttype 1 ✕ type 2/3	✓ type 1 (with MAA) ✓ type 2/3 (with MAA)
Onasemnogene abeparvovec (HST15)	✓ pre-symptomatic ✓ type 1 ✕ type 0 ✕ type 2/3 ✕ progressed type 1 requiring permanent ventilation	N/A	✓ pre-symptomatic (with MAA) ✓ type 1 (without MAA)
Risdiplam (TA755)	✓ type 1 ✓ type 2/3 ✕ pre-symptomatic	✓ type 1 ✕ type 2/3	✓ type 1 (with MAA) ✓ type 2/3 (with MAA)

Abbreviations: CEA = cost-effectiveness analysis; EoL = end-of-life criteria; MAA = managed access agreement; N/A = not applicable; SMA = spinal muscular atrophy

6 Discussion

This review demonstrated that the appraisals of nusinersen, onasemnogene abeparvovec, and risdiplam have mostly captured relevant costs and benefits. Nonetheless, there are critical outstanding issues that relate to the classification of SMA health states, survival modelling, the collection and quantification of resource use data, patient utility values, caregiver utility values, and the incorporation of additional utility values for patients on treatment compared to BSC. Achieving a consensus on how these issues should be approached in economic evaluations for SMA can enable more consistency across appraisals.

6.1 Classification of SMA health states

The current SMA classification system assigns patients to different SMA types (0-4) based on the age of symptom onset and the attainment of motor milestones [57]. Disease severity and life expectancy differ by SMA type [58]. This classification system was used in all three appraisals. However, due to the availability of treatments and advances in technologies used for supportive medical care, extended survival and improved motor function of SMA patients result in a changing natural history of SMA and new phenotypes, particularly if patients are treated pre-symptomatically [57, 59, 60]. Similarly, the possibility of treating SMA type 1 patients may lead to an increase in prevalence of potentially milder SMA phenotypes which has implications for resource use in healthcare systems, including in relation to the type and amount of medical care needed by patients [58, 59, 61]. The committee acknowledged the limitations of the current classification system in all appraisals and was aware that due to the blurry and subjective boundaries delimiting SMA types, the full extent of the disease might not be reflected [34-36].

Given these limitations, it has been proposed to classify SMA phenotypes according to motor function status and their response to therapy, with patients being considered non-sitters, sitters and walkers [57]. Thereby, disease severity is considered on a continuum on which both improvement and deterioration is possible [57, 62]. While the adoption of a revised SMA classification system has the potential to reflect a patient's motor function status more accurately, it also may have

implications for economic modelling. This issue is particularly interesting because NICE's Managed Access Oversight Committee (MAOC) recently decided to extend nusinersen treatment from ambulant type 3 SMA patients also to non-ambulant type 3 SMA patients thereby overturning the initial negative recommendation of the External Assessment Centre (EAC) [63]. One reason for this decision was that, given that the biology of SMA is the same for all patients, the SMA classification system was not created with the intention to differentiate between patients to inform commissioning decisions [63]. Rather than being a barrier for patients to access treatment, it was argued that the classification system should help improve understanding of SMA states [63]. Further, it was acknowledged that despite the heterogenous phenotype of type 3 SMA, creating further smaller subgroups within SMA types would lead to challenges in future re-appraisals as the size of the relevant patient group reduces [63]. Against this background, reaching a consensus on a revised classification system that can be used as a basis for economic evaluations would be beneficial. Similarly, a consensus on model structure, including relevant health states and appropriate approaches to assess motor milestones, would improve consistency and comparability of economic evaluations for SMA both within and across countries.

6.2 Long-term survival

This review highlighted the uncertainty associated with modelled long-term survival outcomes for conditions with relatively small patient populations. It confirms that predicting survival outcomes for rare disease patients is challenging because data available for modelling is typically limited by small sample evidence from short-term clinical trials. For example, in the original risdiplam model for type 1 patients, the choice of the survival distribution and associated parameter estimates was based on only eight events for event-free-survival and five events for OS from the FIREFISH trial [46]. Additionally, follow-up of patients in the pivotal studies for all three treatments was short and thus long-term survival estimates remained uncertain [34-36]. It is not uncommon in such circumstances to look to real-world-data (RWD) for assistance, particularly when MAAs are an increasingly important feature of the commissioning of new technologies. An integral part of the recommendation for nusinersen, onasemnogene abeparvovec and risdiplam was the requirement to follow the conditions of the MAA. While observational data collection in MAAs will contribute to improved knowledge of SMA as a disease, its management, and the disease-modifying treatments available, further data collection from ongoing clinical trials as required in the MAA for onasemnogene abeparvovec and risdiplam may potentially provide more robust survival evidence. Experience with the Cancer Drugs Fund in England also suggests that longer follow-up of trial participants contributes much more to reducing uncertainty regarding survival than real world data collection [64].

6.3 Collection and quantification of resource use data

To estimate resource use and health state costs for SMA, Biogen performed a RWE survey for its nusinersen models [40]. Because it remains challenging to determine the value of RDTs based on their limited clinical evidence [65], in recent years, there has been a growing interest by both regulatory agencies and HTA bodies in the use of RWD to generate RWE to confirm the value of a drug [66, 67]. Thus, RWE studies are useful to inform HTA decisions due to their potential to reduce uncertainties in the evidence base. In this context, NICE has also recently launched a RWE framework as guidance for the development and use of different RWE data types, including resource use and costs [68], which should be taken into consideration when devising further studies for resource use in SMA patients. Another costing issue was the absence of age-adjusted health state costs in the models. In the onasemnogene abeparvovec appraisal, the EAG's clinical experts stated that the assumption of constant costs over a lifetime horizon was not reasonable, rather health state costs would potentially increase with age due to poorer mobility [47]. However, the manufacturer stated

that age-dependent costs were not included due to the lack of evidence for variation in costs by age and the EAG agreed [47]. Nonetheless, a significant economic burden is associated with rare diseases [69], and it is estimated that rare disease average per person per (PPP) year costs are approximately 3-5 times higher than for a healthy age-matched control [70]. Even though PPP year direct medical costs are higher for type 1 SMA patients than for other SMA types [12], it remains unclear to what extent SMA patients who already received treatment, for example with onasemnogene abeparvovec, will incur costs as they age and how the burden on the healthcare system changes. The absence of age-adjusted costs also exemplifies the lack of robust longer-term data which adds uncertainty to the model results.

6.1 Patient health state utility values

The three appraisals for SMA reflect some of the challenges associated with measuring robust utility values for rare conditions. This review supports the findings of a recent systematic literature review demonstrating the absence of robust utility data for SMA [19]. Moreover, as utility measurement instruments are typically designed for adults, validated measures for pediatric patients are often lacking [71]. While NICE recommends the generic EQ-5D measure to estimate HRQoL in adults, no specific measure is recommended for children and adolescents [72]. Nonetheless, NICE stipulates that a validated generic preference-based measure should be used if suitable [72]. It has been argued that the value set of the EQ-5D-Y (the version of the EQ-5D for children and adolescents) should be used in future SMA utility studies [19]. While the EQ-5D-Y uses more child-friendly wording, its five dimensions are still the same as those in the EQ-5D-3L which was developed for adults [73]. Thus, it can be questioned if it is appropriate for children and adolescents to indicate their health using dimensions which were developed for adults, as the way children describe their health may be different. Moreover, at least for decision-making in England, it is a limitation that the available value sets for the EQ-5D-Y are based on how adults in Japan, Slovenia, and Spain value the health of a hypothetical ten-year old child [74].

Among the three RDTs analyzed in this study, HRQoL data from clinical trials was only available from type 2/3 clinical trials for nusinersen and risdiplam. However, the EQ-5D-5L data collected in the SUNFISH trial which was mapped to the -3L format (risdiplam) and the PedsQL data collected in the CHERISH trial which was mapped to EQ-5D-3L using a published algorithm (nusinersen) were not included in the final models due to limited face validity of the estimates [38, 39]. Moreover, different published studies, estimates by the EAG's and the manufacturer's clinical advisors, and Novartis' de novo UK utilities study to inform the onasemnogene abeparvovec models were considered as potential sources for patient utility values. This reflects that even though different techniques to estimate utility values for rare disease patients exist, there is no consensus about the most appropriate method [18], including for SMA.

Further, there is the tendency to accept the use of non-preference-based utility values for modelling SMA. Utility values proposed by the manufacturer's clinical experts in TA588 were also used in the risdiplam models [40, 42]. Further, a non-preference-based utility value based on the opinion the EAG's clinical experts in TA588 was also used in the onasemnogene abeparvovec model for the sitting state, while preference-based utility values were used in other states [37]. While the EAG preferred using either preference-based or non-preference-based utility values for type 1 and type 2/3 patients in the risdiplam models [46], the use of both preference-based and non-preference-based utility values in different states in the onasemnogene abeparvovec model was not highlighted by the EAG. However, utility values for all model health states should usually be derived from the same data source and collected by the same measurement instrument [75]. With regards to the utility values generated by clinical experts, it is important to note that NICE stipulates that if it is not possible to measure HRQoL in patients, data should be obtained from caregiver rather than clinicians [72]. In

addition, NICE recommends that the valuation of health states should reflect public preferences [72]. Both requirements are not fulfilled when estimates proposed by clinical experts are used in economic modelling.

6.2 Caregiver health state utility values

Based on the results of this review it continues to be unclear whether and how caregiver utility, including the impact of bereavement, should be valued in economic evaluations assessed by NICE. A recent systematic literature review to assess economic evaluations in SMA also identified differing approaches regarding the inclusion of caregiver utility values across economic evaluations [62]. Among the three RDTs analyzed here, caregiver utility (implemented as a disutility) was included in the final models for nusinersen [40] and risdiplam [44]. It was excluded in the onasemnogene abeparvovec appraisal because no robust estimates were available according to the manufacturer [37]. So far, NICE guidelines stipulate that caregiver utility can be included in the analyses but is not necessarily required [72]. However, given that the inclusion of caregiver utility can substantially increase the ICER as shown in the present appraisals for SMA, the issue of how caregiver utility should be valued can be decisive in determining whether treatments are cost-effective or not. Thus, while the importance of caregiver utility was acknowledged in all three appraisals, it remains unclear whether NICE have a preferred approach. As such, uncertainty remains about how this issue should be approached by manufacturers developing NICE appraisal submissions for SMA, a disease which has a severe effect on individuals surrounding the patient. Therefore, to increase consistency among appraisals, it could be useful to provide guidance whether or not, and if so how caregiver utility should be valued in SMA, severe diseases more broadly, or in the context of pediatric populations where a larger caregiver burden may be expected. Alternatively, reference cases could be specified that include analyses conducted both with and without caregiver utility. Such guidance should be evidence-based, and ideally preceded by further research examining, for example, the potential caregiver HRQoL improvement from already funded interventions, the evidence and impact of caregiver HRQoL across diseases and clinical areas, and the measurement and sources of caregiver HRQoL [76, 77]. In the absence of official guidance by HTA bodies, recommendations by Pennington et al. [78] may be considered.

6.3 Incorporation of additional utility values for patients on treatment compared to BSC

For all RDTs the potential exists for benefits which are not reflected in the model structure, but there is no consensus on how additional utility for patients on treatment should be modelled to account for these benefits. For onasemnogene abeparvovec and risdiplam additional utility gains were applied [37, 44]. Nonetheless, the manufacturer's approach used to model these gains was only accepted by the committee in the onasemnogene abeparvovec appraisal [36] but not in the risdiplam appraisal [35]. For nusinersen, no additional on-treatment utility was added, even though the committee agreed that certain benefits of gaining specific motor skills might not have been captured in the utility values [34]. Therefore, it could be useful to provide guidance on how additional on-treatment benefits should be modelled, particularly when the model health states and associated utility values are not able to reflect achievement of these benefits. This could prevent situations such as with the risdiplam models in which utility values were amended to account for uncaptured benefits of risdiplam, but eventually resulting utility values for each health state were considered implausible by the committee [35].

7 Conclusion

This study has analyzed the differences and similarities in the NICE appraisals for nusinersen, onasemnogene abeparvovec and risdiplam, and discussed critical outstanding issues across the three economic evaluations. It sought to contribute to the development of evidence that can be used as

guidance for resource allocation decisions for rare diseases. The findings can inform HTA bodies about approaches for the generation, analysis, and interpretation of economic modelling evidence for RDTs for SMA specifically. As many issues discussed here are also recurring across appraisals for other rare diseases, this review may also be useful for stakeholders in the rare disease appraisal space more generally. To facilitate decision-making for RDTs for SMA, increased consistency in economic modelling is needed. In this context, further analyses could focus on the extent to which new evidence, for example from respective MAAs, reduces uncertainties in economic modelling. In addition, comparative studies of how uncertainties in economic modelling for SMA are considered in HTA processes in different countries merit investigation.

8 Expert opinion and five-year review

The advances in the development of disease-modifying treatments provides SMA patients with different active treatment options. As clinical evidence has demonstrated that early treatment, ideally pre-symptomatically, results in better outcomes, patients eligible for treatment could be identified using new-born screening. While new-born screening is currently not routinely available in England [79], genetic testing is offered to siblings of a child that has received a diagnosis of symptomatic SMA [36]. However, a population-based new-born screening study has been initiated in 2022 [80]. The availability of a screening program and the possibility for subsequent treatment may also reduce the prevalence of severe SMA types and result in more SMA patients with potentially milder phenotype and a longer lifespan. This may also change the nature of the demand for healthcare resources required by these patients. However, due to the uncertainty surrounding long-term outcomes in all available treatments, the implications for patient health and resource use in healthcare systems in the future remain unclear.

Moreover, in its updated manuals covering methods, processes and topic selection which have been published by NICE early 2022, a new severity modifier replacing the EoL criteria has been introduced [72]. It remains to be seen how the severity modifier will be used in guidance reviews or future appraisals of SMA treatments. Currently, clinical research focuses on how the consequences of SMN loss in patients can be addressed, particularly with therapeutic agents that are in development or are already approved for other neuromuscular diseases [81]. This also includes therapies for milder phenotypes, for example the SMN-independent asset SRK-015 which is currently being tested in a phase 3 trial for later-onset SMA patients receiving nusinersen or risdiplam [82, 83]. Thus, as future treatment options may include combinations of both SMN-based and SMN-independent treatments, HTA bodies will most likely face more complex economic modelling and appraisals for SMA in the future. Moreover, it is possible that future SMA treatments may qualify for managed access through the recently launched Innovative Medicines Fund (IMF). Having a similar set-up as the Cancer Drugs Fund (CDF), the IMF aims to fund innovative, non-oncology health technologies while further data is collected [84]. Lastly, there is an ongoing debate about how gene therapies, some of which promise potentially life-long benefits, should best be evaluated by HTA bodies. In the case of onasemnogene abeparvovec the committee decided to apply a reduced discount rate of 1.5% to benefits and costs to reflect the impact of the potential treatment benefits. However, whether this approach is also taken for future appraisals of gene therapies most likely depends on the strength of the evidence submitted by the manufacturer. As robust HTA processes can facilitate an efficient and equitable use of scarce healthcare resources, HTA can help maximize health outcomes of rare disease patients in the context of budget constraints and ultimately contribute to better health and wellbeing overall.

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Authors contributions

Both authors contributed to conceptualising and designing the study. LW analysed the data and drafted the protocol manuscript. JC revised the manuscript for important intellectual content and contributed to the methodology. The authors read and approved the final version of the manuscript.

Data availability statement

The data that support the findings of this study are available in the NICE technology appraisal guidance and the NICE highly specialized technology guidance at https://www.nice.org.uk/guidance, reference number TA588, TA755, and HST15. Data was derived from the following resources available in the public domain: https://www.nice.org.uk/guidance/ta588/history, https://www.nice.org.uk/guidance/hst15/history, https://www.nice.org.uk/guidance/ta755/history.

Supplementary material

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