UK National Screening Committee

Review of modelling studies and cost-effectiveness analyses of newborn screening for spinal muscular atrophy

External review against programme appraisal criteria for the UK National Screening Committee

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The UK National Screening Committee secretariat is hosted by the Department of Health and Social Care

UK National Screening Committee

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UK National Screening Committee

Plain English summary

Spinal muscular atrophy (SMA) is a genetic disease that makes muscles weak. It can get worse over time. SMA can be fatal if it affects the muscles that control breathing. There are several types of SMA from 0 to 4. The diagnosis of SMA types is based on the age when symptoms start. For example SMA type 1 develops in babies less than 6 months old and is the most severe form. SMA type 4 affects adults and usually only causes mild problems.

5q SMA is the most common form of SMA. People with 5q SMA have two faulty copies of the *SMN1* gene. This means they are unable to produce enough SMN protein to have healthy motor neurons. A second gene, *SMN2*, also has a role in producing some SMN protein but does not produce enough to replace the faulty *SMN1* gene. People can have between 0-8 copies of the *SMN2* gene (*SMN2* copy numbers). In general people with more SMN2 copies have less severe SMA symptoms. But *SMN2* copy numbers alone does not accurately predict the type or severity of SMA.

There are now three treatments available for patients with SMA. Two, nusinersen (Spinraza) and risdiplam (Evrysidi) are ongoing treatments. The third treatment, onasemnogene abeparvovec (Zolgensma), is a gene therapy.

In 2018 the UK National Screening Committee (NSC) decided that there was not enough evidence to introduce a screening programme in the UK. Since then, two new treatments have been approved for use in the UK. There is also more evidence on the benefits of treatment in pre-symptomatic patients. Other countries have now started screening newborns for SMA. Newborn screening (NBS) allows babies to be diagnosed before they show signs or symptoms. This means it is not possible to know which type of SMA they have before treatment starts. In these babies the number of *SMN2* copies is used to help guide treatment decisions

The NSC uses a set of criteria to make a decisions on whether a condition should be screened for. This review aims to look at the evidence for one of the criterion.

Criterion 14: The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money). Assessment against these criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.

This criterion ensures that a new screening programme is value for money. This is important to ensure that a healthcare budget provides the greatest amount of benefit. Economic analyses often use economic models. These models allow evidence from different sources to be combined together. They also allow for uncertainty to be explored which is especially important for rare diseases.

The aim of this review was to look for economic evidence of NBS for SMA to see if they provide enough evidence to meet the criterion. The review found eight studies from six different countries, including England and Wales. Three of these studies were fully published, that is they had been reviewed by experts and published in an academic journal. One was a pre-print, it had been submitted to an academic journal but had not yet been reviewed by experts or published. Four had only been published as a conference abstract and so only provided a short summary of the study.

The review found that newborn screening for SMA with treatment was generally considered value for money (cost-effective) or cost saving in certain scenarios. This was the case when screening was compared to no screening and treatment. But the studies had not addressed important uncertainties that could impact the results. These include:

- How the number of *SMN2* copies relate to the SMA types
- The models did not include patients diagnosed before showing symptoms without screening, e.g. due to a family history of the disease. These patients would not benefit from screening
- The choice of the current treatment used in the absence of screening has a large impact on the results. There is uncertainty over which treatments to include. The economic models did not compare all potential treatment options
- The long-term effectiveness of the treatments is uncertain. The economic models did not include this uncertainty
- There is uncertainty on outcomes and treatment options for certain sets of patients. This includes patients with 4 or more *SMN2* copies. And it also includes those who are were diagnosed because of screening but who developed symptoms before they started treatment.

The review identified a number of uncertainties that could impact the results. Further work is required to address these. This work includes identifying the best sources of data. And also developing a new economic model to ensure all relevant uncertainties can be easily assessed.

Criterion 14 is still uncertain following this review

Executive summary

Purpose of the review

The aim of this review is to describe existing cost-effectiveness and decision analytics modelling studies of newborn screening (NBS) for spinal muscular atrophy (SMA) in the era of disease modifying treatments. The objective is to inform the UK National Screening Committee (NSC) on the adequacy of current economic evidence for policy making and to inform the development of a model specification for the NSC should that be required.

Background

SMA is an autosomal recessive disease. It involves degeneration of the alpha motor neurons in the spinal cord, leading to symmetrical muscle weakness, atrophy and paralysis in late-stage disease of the most severe types. The impact upon the muscles used to support breathing can have lethal consequences. SMA is traditionally categorised into five different types according to the age of symptom presentation and diagnosis, from type 0 (the most severe, identified at birth) to type 4 (becoming symptomatic in adulthood and usually constituting mild disease). Type 1 (presenting between birth and 6 months of age), also referred to as Werdnig-Hoffman disease, is the most common, accounting for approximately 50% of cases of SMA.

Most cases of SMA are caused by mutations in survival motor neuron *(SMN)* genes. The *SMN1* gene is in the chromosome region 5q, and people with two faulty copies of the *SMN1* gene have 5q SMA. The vast majority of cases (95%) are due to a homozygous deletion of both alleles of the *SMN1* gene in exon 7 (and exon 8 in the majority of cases). Other causes include mutations in the *SMN1* gene, or "compound heterozygotes" where one copy of *SMN1* is deleted and the other has a mutation leading to loss of function. Overall, these genetic changes lead to a decrease in functional SMN protein and ultimately lead to patients developing SMA. A person with one faulty copy of the *SMN1* gene will not have SMA but is a carrier for the condition.

The related *SMN2* gene can also make SMN protein but due to a genetic difference in the gene, only around 10% of the SMN protein from the *SMN2* gene is functional. Therefore, *SMN2* can partially compensate for deletions or mutations in *SMN1*. People can have multiple copies of the *SMN2* gene, with a higher number of *SMN2* copies generally correlating with reduced disease severity. However, it is not currently possible to accurately predict severity or type from genetic information alone.

Three disease modifying treatments are now available in the UK:
Nusinersen (Spinraza, Biogen Idec) is an antisense oligonucleotide designed to modify the product of the *SMN2* gene to produce more functional SMN protein.

- Nusinersen was recommended by the National Institute for Health and Care Excellence (NICE) in 2019 for treatment of 5q SMA, including SMA types 1, 2 or 3, **or** presymptomatic SMA, subject to a managed access agreement (TA588).
- Nusinersen was also recommended by the Scottish Medicines Consortium (SMC) for treatment of symptomatic type 1 5q SMA, and also for types 2 and 3 SMA (the latter from July 2019 for up to 3 years while further evidence is generated).

Risdiplam (Evrysdi, Roche) is a small molecule drug that targets the *SMN2* gene to produce more SMN protein.

- Risdiplam was recommended by NICE in 2021 for treatment of 5q SMA in people aged 2 months and older with a clinical diagnosis of SMA types 1, 2 or 3, **or** presymptomatic SMA and 1 to 4 *SMN2* copies, subject to a managed access agreement (TA755).
- Risdiplam is also recommended by the SMC in Scotland for treatment of 5q SMA in patients aged 2 months and older with a clinical diagnosis of SMA types 1, 2 or 3, **or** with 1 to 4 *SMN2* copies.

Onasemnogene abeparvovec (Zolgensma; Novartis Gene Therapies) is a gene therapy product which expresses the SMN protein.

- Onasemnogene abeparvovec was recommended by NICE in 2021 for treatment of 5q SMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of type 1 SMA in babies aged 6 months or younger (or aged 7 to 12 months if their treatment is agreed by the national multidisciplinary team), if permanent ventilation for more than 16 hours per day or a tracheostomy is not needed, and subject to a commercial arrangement. It was also recommended for presymptomatic 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene in babies, subject to a managed access agreement (HST15).
- A partial review of NICE HST15 in 2023, focussing on presymptomatic SMA, has published draft guidance with similar recommendations: a draft recommendation of onasemnogene abeparvovec for presymptomatic 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene in babies aged 12 months and under, subject to a commercial arrangement.
- Onasemnogene abeparvovec is also recommended by the SMC in Scotland for treatment of 5q SMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA type 1, **or** presymptomatic 5q SMA patients with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene (where patients are expected to develop SMA type 1).

Focus of the review

The current review aims to appraise the evidence related to criterion 14.

Criterion 14: The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie. value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.

Modelling studies are available. However, it the applicability to the UK and the quality of the studies is unclear. The purpose of this review of existing modelling studies is to help the UK NSC develop a model and, in particular, to stimulate discussion with stakeholders on key issues that will inform a modelling and cost effectiveness project in the future.

No previous reviews have addressed this criterion or question.

Recommendation under review

The UK NSC recommendation is that a universal screening for SMA should not be introduced.

The most recent UK NSC review process was completed in 2018. This addressed prenatal genetic carrier screening, antenatal screening and newborn screening. In relation to newborn screening the review reported that:

- There was still insufficient information about the incidence and prevalence of SMA, or how many people are affected by each type of SMA (and in consequence what level of severity) in the UK.
- Four studies reported on SMA newborn screening tests. Two studies found that mCOP-PCR and HRM analysis are highly sensitive and specific newborn SMA screening methods. However, overall the evidence base had a high or unclear risk of bias and it was mainly based on small population screening studies, in populations that might not reflect the general population.
- Only one treatment, nusinersen (which is marketed as Spinraza™), was found showing promising results suggesting that nusinersen is effective in improving outcomes for patients with SMA. Two high-quality RCTs reported better outcomes on measures of motor control in patients with infantile-onset and later-onset SMA given nusinersen compared to sham control. However, the evidence base was limited with studies still ongoing, and therefore, there was a lack of data for the long-term effectiveness and safety of the treatment.
- There was no high-quality evidence for an optimal management pathway for SMA patients identified through screening, so the benefits of pre-symptomatic treatment compared to treatment following symptom onset were unclear.

Criterion 14 has not previously been reviewed.

Findings and gaps in the evidence of this review

Criterion 14 is still uncertain following this review

Eight individual studies, from 14 reports, were identified in the review. The review included three full cost-effectiveness studies with fully published papers: one from the US, one from Australia one from the Netherlands. It also included one preprint of a full cost-effectiveness study from England and Wales. Four cost-effectiveness studies with conference abstracts only were also included: two from the US, one from Italy, and one from Belgium

The included studies found NBS followed by treatment with a disease modifying treatment, in particular onasemnogene abeparvovec, is generally cost-effective or cost saving when compared to no NBS and treatment with disease modifying treatment. However, there are several key uncertainties that have not been fully addressed in any of the included models including the mapping of SMA genotypes (number of copies of the *SMN2* gene) to phenotypes (SMA types) and issues around choice of treatment mix in both arms of the model, treatment price, and long-term effectiveness. Furthermore, no study considered pre-symptomatic treatment through a family history in the non-screened arm of the model.

Recommendations on screening

Based on the review there is not currently sufficient credible modelling evidence on the cost-effectiveness of NBS for SMA in the UK. While the results of the included models indicate that N

BS is generally cost-effective or costs saving important uncertainties have not been fully addressed. These include:

- The mapping of the SMA genotypes (*SMN2* copies) to SMA phenotypes (SMA Types) to ensure the population in both arms of the model have the same distribution of disease severity
- The inclusion of pre-symptomatic treatment in the non-screened arms for patients who have a family history of the disease
- More comprehensive scenarios including pairwise comparisons between all treatment options and best supportive care as well as varying the included treatment mix. Two of the three treatments are only available in England and Wales under managed access agreements and may not therefore represent standard care.
- Additional sensitivity analyses on the long-term effectiveness of the included treatments
- Clearer assumptions on the treatment of patients with 4 or more *SMN2* copies or who were screened but were symptomatic prior to treatment
- Further validation of the health state costs and quality of life values and use of the most recent studies

It is unclear what the impact of addressing all these uncertainties will be on the cost-effectiveness results. Therefore, further work is needed to identify the best sources of data to address these uncertainties this may involve systematic reviews, validation of existing data, or the use of expert or patient opinion. Given the number of uncertainties, a new cost-effectiveness model may be needed to ensure all relevant uncertainties can be easily assessed.

Limitations

Papers were screened by a single reviewer, with a second reviewer checking 20% of the total and any uncertain papers. Data was extracted by a single reviewer.

Not all studies included a fully published paper. To ensure the most up to date evidence was captured we have included a pre-print paper that has not yet undergone peer review and conference abstracts. However, we are aware of at least one additional study that was only included as a conference abstract in this review that is in the process of submission to a journal. This study (1) has used data and costs from patients who have undergone screening and may offer further relevant evidence.

Evidence uncertainties

Further work is needed to identify the best sources of data to address the outlined uncertainties. This may include systematic reviews, validation of existing data, or the use of expert or patient opinion. Given the number of uncertainties, a new cost-effectiveness model may be needed to ensure all relevant uncertainties can be easily assessed.

UK National Screening Committee

Introduction and approach

Background

Spinal muscular atrophy (SMA) is an autosomal recessive disease. It involves degeneration of the alpha motor neurons in the spinal cord, leading to symmetrical muscle weakness, atrophy and paralysis in late-stage disease of the most severe types. The impact upon the muscles used to support breathing can have lethal consequences. SMA is traditionally categorised into five different types according to the age of symptom presentation and diagnosis, from type 0 (the most severe, identified at birth) to type 4 (becoming symptomatic in adulthood and usually constituting mild disease). Type 1 (presenting between birth and 6 months of age), also referred to as Werdnig-Hoffman disease, is the most common, accounting for approximately 50% of cases of SMA.

Most cases of SMA are caused by mutations in survival motor neuron *(SMN)* genes, which code for the SMN protein. The *SMN1* gene is in the chromosome region 5q, and people with two faulty copies of the *SMN1* gene have 5q SMA. The vast majority of cases (95%) are due to a homozygous deletion of both alleles of the *SMN1* gene in exon 7 (and exon 8 in the majority of cases). Other causes include mutations in the *SMN1* gene, or "compound heterozygotes" where one copy of *SMN1* is deleted and the other has a mutation leading to loss of function. Overall, these genetic changes lead to a decrease in functional SMN protein and ultimately lead to patients developing SMA. A person with one faulty copy of the *SMN1* gene will not have SMA but is a carrier for the condition.

The related *SMN2* gene can also make SMN protein but due to a genetic difference in the gene, only around 10% of the SMN protein from the *SMN2* gene is functional. Therefore, *SMN2* can partially compensate for deletions or mutations in *SMN1*. People can have multiple copies of the *SMN2* gene, with a higher number of *SMN2* copies generally correlating with reduced disease severity. However, it is not currently possible to accurately predict severity or type from genetic information alone.

Current policy context and previous reviews

The UK National Screening Committee (NSC) currently recommends against screening for SMA. The Committee based this recommendation on the evidence provided by the 2018 review carried out by Costello Medical on behalf of the UK NSC. The 2018 review of screening for SMA followed the methodology for an evidence review. The review assessed three types of screening for 5q SMA: newborn screening, carrier screening and antenatal screening. The review also sought evidence on the effectiveness of pharmacological treatment for SMA.

In terms of screening, the 2018 review did not identify any prospective studies relating to carrier or antenatal screening; these are not the focus of the current review and are not discussed further. In terms of newborn screening, the 2018 review identified four publications reporting on five studies. Three were case-control studies, which may not be reflective of a general screening population (2–4). Two were cohort studies, one in Taiwan which screened 120,000 newborns (5), and one in China which screened 2,000 stored DBS samples rather than a live population(4). The review concluded that it was not yet possible to robustly quantify the accuracy of newborn screening methods.

In terms of treatment, five randomised controlled trials (RCTs) were found by the 2018 review to report outcomes of treatment for SMA. All related to treatment of symptomatic patients. Two RCTs suggested that nusinersen is effective compared to sham control in improving outcomes for patients with symptomatic SMA. In addition, olesoxime, valproic acid and somatropin were investigated in one RCT each but were not found to be effective treatments for SMA. The review concluded that there was still insufficient evidence that presymptomatic treatment is more beneficial than usual care, and there was also a lack of long-term efficacy and safety data.

Since the 2018 UK NSC evidence summary, the SMA screening landscape has changed significantly with a number of countries introducing pilots or implementing NBS for SMA and additional disease modifying treatments.

In the UK, there are now three main treatments available for SMA as follows.

Nusinersen (Spinraza, Biogen Idec) is an antisense oligonucleotide designed to modify the product of the *SMN2* gene to produce more functional SMN protein.

- Nusinersen was recommended by the National Institute for Health and Care Excellence (NICE) in 2019 for treatment of 5q SMA, including SMA types 1, 2 or 3, **or** presymptomatic SMA, subject to a managed access agreement (TA588).
- Nusinersen was also recommended by the Scottish Medicines Consortium (SMC) for treatment of symptomatic type 1 5q SMA, and also for types 2 and 3 SMA (the latter from July 2019 for up to 3 years while further evidence is generated).

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- Risdiplam is also recommended by the SMC in Scotland for treatment of 5q SMA in patients aged 2 months and older with a clinical diagnosis of SMA types 1, 2 or 3, **or** with 1 to 4 *SMN2* copies.

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- A partial review of NICE HST15 in 2023, focussing on presymptomatic SMA, has published draft guidance with similar recommendations: a draft recommendation of onasemnogene abeparvovec for presymptomatic 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene in babies aged 12 months and under, subject to a commercial arrangement.
- Onasemnogene abeparvovec is also recommended by the SMC in Scotland for treatment of 5q SMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA type 1, **or** presymptomatic 5q SMA patients with a bi-allelic mutation in the *SMN1*

gene and up to 3 copies of the *SMN2* gene (where patients are expected to develop SMA type 1).

In addition, a small UK case control (two gate) study of the accuracy of polymerase chain reaction (PCR) based screening has been undertaken and published (6). This is being followed up with a large cohort study of the accuracy and feasibility of PCR based screening in the UK. Because of this, the quality of test accuracy data from the UK will be improved in comparison with most other UK NSC reviews.

These, and other, developments were discussed at a UK NSC stakeholder workshop in July 2021. It was noted that the UK NSC needs to review the evidence relating to newborn screening for SMA as part of its triennial review cycle. The recent developments suggest that evidence maps, or evidence summaries alone may not be appropriate products for the forthcoming review and that a more comprehensive statement on the effectiveness of screening for SMA is needed. In the absence of direct trial evidence, the UK NSC is increasingly using decision analytic models for this purpose in its work on rare diseases.

There has been no previous review of cost-effectiveness and decision analytic modelling studies of newborn screening for SMA.

Objectives

The aim of this evidence summary is to conduct a review of the available cost-effectiveness and decision analytic modelling studies of newborn screening for SMA in the era of novel treatments to inform the development of a model for the UK NSC and discussion on the key issues. To answer the key question: How have modelling studies and cost-effectiveness analyses addressed newborn screening for SMA in the era of novel treatments.

Table 1: Key questions for the evidence summary and relationship to the UK N S C screening criteria

	Criterion	Key questions	Studies Included
14	The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie. value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.	How have modelling studies and cost effectiveness analyses addressed newborn screening for SMA in the era of novel treatments?	8 studies from 11 papers

Methods

The current review was conducted by ScHARR in collaboration with the UK NSC, in keeping with the UK National Screening Committee evidence review process. Database searches were conducted on 25 November 2022 to identify studies relevant to the questions detailed in Table 1.

Eligibility for inclusion in the review

The following review process was followed:

1. Each abstract was reviewed against the inclusion/exclusion criteria by one reviewer. Where the applicability of the inclusion criteria was unclear, the article was included at this stage to ensure that all potentially relevant studies were captured. A second independent reviewer provided input in cases of uncertainty and validated 20% of the first reviewer's screening decisions. Any disagreements were resolved by discussion until a consensus was met.
2. Full-text articles required for the full-text review stage were acquired.
3. Each full-text article was reviewed against the inclusion/exclusion criteria by one reviewer, who determined whether the article was relevant to one or more of the review questions. A second independent reviewer provided input in cases of uncertainty. Any disagreements were resolved by discussion until a consensus was met.

Eligibility criteria for each question are presented in Table 2 below.

Table 2: Inclusion and exclusion criteria for the key questions

Key question	Inclusion criteria							
	Population	**Target Condition**	**Intervention**	**Comparator**	**Outcomes**	**Study Design**	**Setting**	**Language**
1	Newborns		Newborn screening for SMA	No newborn screening	Total cost of screening for SMA	Decision analytic models and economic evaluations i.e. studies comparing at least two alternative interventions in terms of costs and outcomes.	UK and International	English Language
				Cascade screening	Incremental cost	Cost-minimization		
					Incremental life-years gained	Cost-effectiveness		
					Gain in other clinical outcomes as defined by the study	Cost-utility		
					Incremental cost-effectiveness ratio (ICER)	Cost-benefit		

		Number of lives saved	Cost-consequence analyses
		Cost per life	Reviews of economic evaluations can also be included.
		Any other outcome as outlined by the study	

Appraisal for quality/risk of bias tool

The reporting quality of the included studies will be assessed using Philips et al (7) checklist for assessing the methodological quality of decision analytic models for health technology assessments

Results of the quality assessments are presented in Summary and appraisal of individual studies; Appendix 3

Databases/sources searched

The search strategy is presented in Appendix 1.

Searches were conducted on 25 November 2022 on the following sources:

- Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to November 23, 2022
- Embase via Ovid 1974 to 2022 November 23
- NHS Economic Evaluation Database (NHS EED) 1994 to March 2015 (Archive only)
- Econlit via Ovid 1886 to November 17, 2022
- Tufts CEA Registry 1976 to present
- MATHSSCINET 1800s to present

Question level synthesis

Criterion 14 — The opportunity cost of the screening programme

The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie. value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.

Question 1 – How have modelling studies and cost effectiveness analyses addressed newborn screening for SMA in the era of novel treatments?

This question was not examined in the previous review in 2018. In the absence of direct trial evidence, the UK NSC is increasingly using decision analytic models for this purpose in its work on rare diseases in order to provide a framework for synthesising evidence from a number of sources.

Modelling studies are available. However, it is unclear if any are applicable to the UK or the quality of the studies. The purpose of this review of existing modelling studies is to help the UK NSC develop a model and, in particular, to stimulate discussion with stakeholders on key issues that will inform a modelling and cost effectiveness project in the future.

Eligibility for inclusion in the review

The inclusion criteria for the review were decision analytic model and economic evaluation i.e. studies comparing at least two alternative interventions in terms of costs and outcomes that evaluated newborns screened for SMA as part of a population level screening programme as part of a population level newborn screening programme followed by treatment from a novel therapy (nusinersen, onasemnogene abeparvovec, or risdiplam). Studies that only considered specific SMA screening populations such as antenatal screening or cascade screening (screening siblings or family members of diagnosed SMA patients) were excluded. Studies had to include both cost and health outcomes for at least two interventions. Reviews of economic evaluations could also be included.

The papers excluded at the full text stage were excluded because they were commentaries on economic analyses (8,9).

Description of the evidence

Database searches yielded 712 results, of which 11 were judged to be relevant to this question. This included five full published papers and six conference abstracts. One of the full papers related only to the costs and quality adjusted life years (QALYs) of SMA patients but was used in the model reported in a conference abstract, two of the full papers related to the same model, and three conference abstracts related to one model. Where multiple papers relate to a single

model, information from multiple papers was used but reported as one study. Therefore, there were three fully published studies and three models reported in conference abstracts.

Hand searching identified two additional studies that were published after the date of the search. This included a preprint of a cost-effectiveness model for England and Wales and a conference abstract for a cost-effectiveness model for Italy.

In total the review includes four full studies and four studies reported in conference abstracts.

Appendix 2 contains a full PRISMA flow diagram (Figure 1), along with a table of the included publications (Table 15).

Discussion of findings

A study-level summary of data extracted from each included publication is presented in 'Summary and appraisal of individual studies Appendix 3'.

Overview

The review included three full cost-effectiveness studies with fully published papers: one from the US (10), one from Australia (11,12), and one from the Netherlands (13). It also included one preprint of a full cost-effectiveness study from England and Wales (14). Three cost-effectiveness studies with conference abstracts only were also included: two from the US (15–18), one from Italy (19) , and one from Belgium (1). The search also identified a full published paper of the cost and utility values that were used in the model from Belgium and data from this study was included where appropriate to supplement the limited data included in the conference abstract (20). For the three other conference abstracts limited data was available.

Of the four full studies two were funded by NovartisGene Therapies, who are the manufacturers of one of the disease modifying treatments, onasemogene abeparvovec (13,14). The other studies were funded by the Luminesce Alliance (11,12) and The Utah Center for Excellence in ELSI Research (UCEER) (10). Funding information is not available for the conference abstracts but author affiliations include NovartisGene Therapies for one study (19) and AveXis who were the original manufacturers of onasemogene abeparvovec for one other (15–17).

Epidemiology

All the studies that stated the incidence of SMA used in the model reported a similar figure of between 0.91 to 1 per 10,000 from a range of different sources.

Limited information was provided on the type and methodology of the screening test and confirmatory testing under consideration. Three studies(11,13,14) specified the type of test (polymerase chain reaction genotyping assay) used. In the Australian study this was only included in the second publication (11) and in one study it was only specified as a footnote to a table (14). Four of the studies included the proportion of patients with a point mutation who would not be identified through screening. Arjunji et al (16), Weidlich et al (14), Velikanova et al (13), included the proportion of 5%, 4%, and 1% respectively. Shih et al (12) included a false negative rate based on the rate found in the screening pilot in Australia to account for patients with a point mutation which works out at around 6% of SMA patients.

All the studies which stated the distribution of SMA types in the model used SMA phenotypes (SMA Types 1, 2, and 3) in the non-screening arm. No studies included type 0 or type 4. One study only included patients with SMA type 1 which was used in both arms of the model (10). Four studies included the distribution of Type 1, Type 2, and Type 3 SMA (12–14,16). These four studies included SMA genotypes based on the number of *SMN2* copies in the NBS arm. As shown in Table 3 the same distribution of SMA types were used in all models but differing distributions of *SMN2* copies were used in the NBS arms. The distribution of patients with *SMN2* copies was taken from data from a NBS pilot for the Australian study (12).

Arjunji et al (16) was the only study that included a mapping of how the number of *SMN2* copies were related to SMA types for the NBS arm. However, when the distribution of SMA types is calculated from the distribution of *SMN2* copies to SMA types it does not match the distribution of SMA types used in the non-screened arm of the model. This indicates that the screened and non-screened modelled population are different with the NBS population having a less severe distribution of disease compared to the non-screened population. This is likely to be an issue for all the models that use difference sources for the distribution of SMA phenotypes and the distribution of *SMN* copies.

All studies that included patients with a point mutation assumed that they would present symptomatically with the same SMA phenotype distribution as in the no-screen arm. The Weidlich et al (14) study included the assumption that 40% of patients with *SMN2* 2 copies would be symptomatic by the time of treatment. It is reported that for these patients they assumed the same distribution of phenotype as in the no screen arm. However, the paper also states that the transition probabilities are based on patients with SMA type 3 for these patients. It is therefore unclear how the SMA phenotype distribution was used for this population.

Table 3: Distribution of SMA phenotypes and genotypes by study

		Arjunji et al (16)	Arjunji et al calculated*	Shih et al (12)	Velikanova et al (13)	Weidlich et al (14)
SMA phenotypes	**SMA Type 1**	58%	39%	58%	58%	58%
	SMA Type 2	29%	21%	29%	29%	29%
	SMA Type 3	13%	40%	13%	13%	13%
SMA genotypes	**SMN2 2 Copies**	45%	-	69%	45%	47%
	SMN2 3 Copies	19%	-	31%	33%	25%
	SMN2 4 Copies	36%	-	0%	22%	28%

*Calculated from the SMA types by *SMN2* copies reported in abstract

SMA, spinal muscular atrophy

Screening and diagnosis

Screening parameters were limited to the costs of the screening test and the proportion of SMA patients with a point mutation for several studies (10,13,14). Arjunji et al (16) included the reflex cost of reflex screening. Shih et al (12) included the proportion of false negatives, the number of screening retests needed due to non-amplification and the percentage who go on to have a further test as well as the costs of the screening test and the costs of a repeat screening test. Two studies included the costs of genetic testing in both arms of the model (13,14). No studies included additional diagnosis costs in the non-screened arm of the model.

Modelled health states

A similar model structure based on motor milestone was reported for three of the full cost-effectiveness studies (12–14), with the Weidlich et al (14) model being based on the Velikanova et al (13) model. These two models (13,14) allowed some transitions to a worse health state whereas the Shih et al (12) model allowed patients one transition to a worse health state and included a separate health state for these patients. Jalai et al (10) did not include a model structure diagram and stated the model health states included included SMA-free, untreated SMA, treated SMA, motor milestones response, Permanent ventilator assistance (PVA), and dead health state.

Treatment mix

Table 4 shows the treatments included in both the NBS and the non-screened arms. The included treatments differed between studies. A treatment mix describes a scenario where a proportion of patients receive each treatment. In studies without a treatment mix it is assumed that all patients in one arm of the model receive the same treatment. Two studies included a treatment mix, with Velikanova et al (13) assuming 94% of patients would receive onasemogene abeparvovec and the rest nusinersen. Weidlich et al (14) varied the treatment mix based on SMA phenotype and genotype. It was the only study to vary the treatment mix based on whether a patient was identified through screening or symptomatically with more patients receiving onasemogene abeparvovec in the screened arm.

Table 4:Treatment options in the included studies

Intervention	Treatment	Study							
		Arjunji et al (16)	Chen et al (18)	Dangouloff et al (1)	Ghetti et al (19)	Jalali et al (10)	Shih et al (12)	Velikanova et al (13)	Weidlich et al (14)
Screening	**BSC**	-	-	-	Unclear	Yes	-	-	Yes
	Nusinersen	-	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Risdiplam	-	-	Yes	Yes	-	-		Yes
	Onasemogene abeparvovec	Yes	Yes	Yes	Yes	-	Yes	Yes	Yes
	Treatment mix	-	-	Unclear	Unclear	-	-	Yes	Yes
No Screening	**BSC**	-	Yes	-	Unclear	Yes	Yes	-	Yes
	Nusinersen	-	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
	Risdiplam	-	-	Yes	Unclear	-	-	-	Yes
	Onasemogene abeparvovec	Yes	-	Yes	Unclear	-	Yes	Yes	Yes
	Treatment mix	-	-	Unclear	Unclear	-	-	Yes	Yes

BSC, best supportive care

Transition probabilities

The transition probabilities between health states varied in all models based on the treatment received and if it was given symptomatically or pre-symptomatically. As there was no data on onasemogene abeparvovec at the time of the study Shih et al (12) assumed the same transition probabilities as nusinersen in the screened arm. All studies referenced the relevant trial studies for the treatment transition probabilities. For best supportive care observational studies were used. From the four full studies, only two reported the transition probabilities used (10,12). No transition probabilities values were reported for the other two studies (13,14). All studies assumed greater treatment effectiveness in patients treated pre-symptomatically.

Most studies that reported the transition probabilities assumed that any gains made during the trial period would be sustained in the long term. Long term survival was then based on the health state a patient occupied at the end of this period. Some models included the possibility of transitions to a worse health state between some, but not all, health states for patients in the best supportive care arm or who did not respond adequately to treatment (12–14).

Weidlich et al (14) was the only study to include a proportion of patients would be symptomatic at the time of treatment in the NBS arm of the model. It is assumed that 40% of patients with *SMN2* 2 copies will be symptomatic before the time they receive treatment. This is in keeping with evidence from the NBS programmes and pilots. Data from patients with SMA Type 3 was used as a proxy for these patients for all treatments. The values used for the transition probabilities were not reported and therefore it is not possible to assess the impact on patient progression that is modelled.

Perspective

Two studies included a societal perspective with Jalali et al (10) including productivity losses and Shih et al (12) including costs of informal care and parents' loss of productivity. Other studies included a societal perspective in a sensitivity analysis with additional costs being included in two (13,14) with one study also included carers quality of life (1).

Resource Use

Most studies included the costs of the screening test but as noted above, only Shih et al (11) included the repeat screening costs. No studies included any implementation or training costs for the screening programme. The only diagnosis costs included were the costs of genetic testing in two studies which were the same in both arms of the model (13,14). This is likely to underestimate diagnosis costs in the no screen arm as it does not account for the 'diagnosis odyssey' that patients may undergo before they receive a diagnosis.

Two studies included costs by health state ((13,14) and were based on a UK health care resource utilisation study which surveyed clinicians. Additional Dutch specific costs were included in the Velikanova et al study (13). Shih et al (12) used costs from an Australian study of the economic burden of SMA which were by SMA type (21). It is unclear how these are applied to the health states within the model. One study included age specific costs (10). The costs by the number of *SMN2* copies and method of diagnosis was included for the Dangouloff study (1,20). Given the differences in approaches, costs by health state and costs by SMA type or number of *SMN2* copies it is not possible to directly compare the costs across the studies.

Treatment costs in all the models included the cost of the drug and administrations costs. For Arjunji et al (16) the costs of onasemogene abeparvovec differed depending on whether it was given to symptomatic or pre-symptomatic patients. Weidlich et al (14) based the treatment costs

and administration costs on UK list prices and NHS reference costs but did not report values. Treatment prices in all other studies were reported and based on country specific list prices where available.

Utilities

Two studies (13,14) used the values used in the NICE appraisals of onasemogene abeparvovec and nusinersen. These were based on clinical experts for the permanent ventilator assistance PVA health state, a cross sectional study of patients with SMA in Europe for the not sitting health state (22), clinical experts who advised the evidence review group for the NICE appraisal of nusinersen for the sitting health state and general population values for the walking and broad range of normal development (BRND) health states.

Shih et al (12) used values from an Australian study on patients before disease modifying treatments were available (21) and supplemented this with data from a US community study for each health state (23). They also included a decrement of 20% for those that 'lose' a health state. The values used are lower than those used in the other studies (13,14) for all health states and unlike the values used are all derived from quality-of-life studies in SMA patients. The impact on results is not clear as QALYs will be lower in both the screened and non-screened arms of the model. Arjunji et al (16) report they used the values from the Institute for Clinical and Economic Review report but do not present the values. Jalali et al (10) did not report utility values by health state but included lifetime utility values based on asthma for those with SMA without PVA and Duchenne with nocturnal ventilation for the PVA health state.

Table 5: Utility values by health state

Health state	Study Weidlich et al (14)	Velikanova et al (13)	Shih et al (12)
PAV	0	0	0
Not sitting	0.19	0.19	0.02
Sitting	0.6	0.6	0.11
Stands (with assistance)	-	-	0.25
Walk with assistance	-	-	0.38
Walking	General population	General population	0.64
BRND	General population	General population	-

PAV, permanent assisted ventilation; BRND, broad range of normal development

While the conference abstracts of the Dangouloff study (1) do not report utility values a paper on the costs and utility values used in the analysis reports utility values by *SMN2* copy number for those diagnosed pre-symptomatically, those treated symptomatically, and those diagnosed symptomatically and not treated (20). The study includes the values from three different utility measures: EQ-5D, HUI2, and HUI3. The results are not directly comparable to the cost-effectiveness models as they are by *SNM2* copy number rather than health state. However, they do show high values, around 1, for the small number of pre-symptomatically detected patients. They also show a difference in utility value for the same *SMN2* copy number depending on the utility measure used. Indicating a consistent utility measure is needed to value all the health states.

Results

There was a range of results depending on the treatment options under consideration and the time horizon of the models. The most common results from the studies was that NBS dominated no screening, that is, NBS resulted in lower costs and higher QALYs than no screening over a

lifetime horizon. Results by individual treatment option are shown in Table 6 and results for studies that used a treatment mix are shown in Table 7.

Two studies compared no screening and best supportive care or nusinersen and NBS with nusinersen or onasemogene abeparvovec (12,18). The Shih et al study (12) found that NBS followed by onasemogene abeparvovec was dominant when compared to no screening with nusinersen. In the Chen et al study (18) NBS followed by onasemogene abeparvovec compared to no screening and nusinersen had an incremental cost-effectiveness ratio (ICER) at $187,650. It was the only study including onasemogene abeparvovec that did not find NBS to dominate no screening. As it is a conference abstract it is not possible to fully compare why this study has a higher ICER than the other studies. The limited results presented suggest there were lower costs in the non-screened nusinersen arm of the model compared to other studies.

Two studies compared a mix of treatments in both arms of model (13,14). Weidlich et al (14) included treatment with onasemogene abeparvovec, risdiplam, nusinersen, and best supportive care. The proportion of patients receiving each treatment differed between SMA phenotype and genotype and whether they were in the screen or non-screened arm of the model with a larger proportion of patients receiving onasemogene abeparvovec in the screened arm of the model. In Velikanova et al (13) 94% of patients were treated with onasemogene abeparvovec and the remaining with nusinersen and is assumed to be the same in both the NBS and non-screened arms of the model. In both studies NBS was found to dominate no screening.

It is unclear which treatment options are included in the Ghetti et al study (19), although trials for all three treatments are referenced. It is also unclear which treatments, and in which proportions, are included in the Dangouloff et al study (1). Ghetti et al (19) found that NBS dominated no screening. Dangouloff et al (1)estimated an ICER of €5,280 per QALY when only medical costs were included, but found NBS dominated no screening when additional costs were included. It was unclear from the abstract what additional costs were included in the total global cost.

Two studies included only one treatment option in the screened and non-screened arms. In the Jalai et al study (10) NBS with treatment with nusinersen was compared to no screening and nusinersen and the ICER was found to be $199,510 per QALY gained. In the Arjunji et al study (16) which included onasemogene abeparvovec only and the ICER was $15,181 per QALY for treating any positive patient. If only patients with ≤3 *SMN2* copies are treated NBS was found to dominate no screening.

The sensitivity analyses found important parameters to be the time horizon of the models (12,14), treatment costs (10,12), treatment mix (13), comparator treatment (10,12), treatment targeting (16), and survival (14). The general population utility intercept was found to be an important parameter in two studies (13,14). For studies that found NBS to dominate no screening the PSA results found that NBS was likely to be cost saving or cost-effective in 100% of runs.

Table 6: Results by screening/no screening and individual treatment option

Study	Intervention Arm	Comparator Arm NBS & Nusinersen	NBS & gene therapy	No NBS & BSC	No NBS & Nusinersen	No NBS & gene therapy
	NBS & Nusinersen					
Shih et al (12)		-	-	$577,000	$513,000	-
Jalali et al (10)		-	-	$226,667*	$ 192,857*	-
Chen et al (18)		-	-	$638,462*	$ 554,167*	-
	NBS & gene therapy					
Shih et al (12)		Dominated (GT less costly but equivalent effectiveness)	-	$216,000	*- $29,000*	-
Arjuni et al (16)		-	-	-	-	$ 521,971
Arjuni et al (16) (limited to ≤3 SMN2 copies)		-	-	-	-	*$- 142,303*
Chen et al (18)		*-£1,945,000**	-	$ 294,000*	$197,143*	-
	No NBS & Nusinersen					
Shih et al (12)		-	-	$ 706,000	-	-
Jalali et al (10)		-	-	$ 546,000*	-	-
Chen et al (18)		-	-	$1,650,000*	-	-

*Results calculated by author based on information in published study. Some results differ to the published results due to rounding in the published total of incremental costs and QALYs

BSC – Best supportive care, NBS – Newborn Screening, - Comparison not reported

Table 7: Results by treatment mix

Study	Treatment mix NBS	Treatment mix no NBS	ICER
Weidlich et al (14)	SMN2 2- 3 copies 93% OA, 6% Nus, 1% BSC SMN2 4 copies 6% Nus, 50% Ris, 44% BSC	SMA Type 1 56% OA, 2% Nus, 22% Ris, 20% BSC SMA Type 2&3 10% Nus, 90% Ris,	*-£117,541*
Velikanova et al (13)	94% OA, 6% Nus	Same as NBS	*-€37,564*
Ghetti et al (19)	Not stated	Not stated	*-€143,167*
Dangouloff et al	Not stated	Not stated	€5,820

BSC – Best supportive care, NBS – Newborn screening, ICER – Incremental cost effectiveness ratio, Nus – Nusinersen, OA - onasemogene abeparvovec, Ris – risdiplam

Limitations and applicability to the UK: Model structure including disease management and structure of the screening programme

Three of the fully published models had a clear model structure based on motor milestones which is similar to the models used and accepted in the NICE appraisals of nusinersen, onasemogene abeparvovec, and risdiplam (24–27). However, apart from Shih et al (12), little detail was included on the structure of the screening programme. No studies included implementation costs of screening and only Shih et al (11) included any screening test characteristics or the proportion of additional tests needed.

There was little reported detail on how well the SMA phenotypes and genotypes, taken from different sources, mapped to each other. As shown from the proportions in the Arjunji et al study (16) assumptions made on these distributions may mean that the population in the screened and non-screened arm consists of patients with a different distribution of disease severity. More detail is needed in all studies on how the distributions were calculated to ensure the distribution of patients is the same in both the screened and non-screened arms of the model. It was also unclear how most models handled treatment options for patients with ≥4 *SMN2* copies given that onasemogene abeparvovec is not licensed in this population in Europe.

None of the studies included pre-symptomatic treatment in the non-screened arm. Patients may be identified pre-symptomatically without screening due a family history of the disease. Including these patients in the base case or as a sensitivity analysis would reduce the cost-effectiveness of NBS.

There is evidence from the pilots of NBS (or implementation) that some patients refuse treatments for their children (28). However, no study included no treatment option for patients in the screened arm (apart from patients with ≥4 SMN2 copies in one study (14)) even as a sensitivity analysis. Any treatment refusal in patients with a lower number of SMN2 copies is likely to reduce the cost-effectiveness of NBS. However, treatment refusal may be reduced by the greater treatment options and evidence on effectiveness of treatments that is now available.

No model included the impact of sibling cascade screening. There may be benefits of testing older siblings of patients identified through NBS and starting them on treatment before they become symptomatic. This is most likely to identify patients with type 2 or 3 SMA as the siblings would generally be at least 1 year old. This benefit would also only apply for the first few years of screening as after that older siblings would themselves have been screened.

Limitations and applicability to the UK: Model parameters including disease epidemiology, treatment mix, resource use and costs, HRQoL, screening test

Relevant trials or observational studies have been used to inform the transition probabilities in all models. Most models assumed that motor milestones achieved by a set endpoint, usually based on the length of the trials, would be sustained and life expectancy was generally based on the achieved motor milestone health state. The assumption of sustained benefit at the end of the trial period has broadly been accepted in the NICE appraisals of the relevant treatments, however, sensitivity analyses including transitions to a worse health state for treated patients were generally included. None of the screening models included this which would have provided a useful analysis given the long-term uncertainties around treatment effectiveness (24–27).

Transition probabilities values were also only reported for two of the studies(10,12). This makes it difficult to assess the assumptions made around treatment effectiveness in the other models. It also makes it unclear what data was used for some of the subgroups within the models. For example, it is unclear what data was used for the transition probabilities for the 44% of the patients with 4 copies of the *SMN2* genes who received best supportive care or those patients who were symptomatic at the time of treatment in the in the Weidlich et al study (14).

The treatment mix approach in the Weidlich et al study (14) is likely to represent treatment patterns in the UK better than the other models as it includes all three currently recommended treatments in England and Wales. However, no sensitivity analysis was conducted on varying the proportions. Previous studies have shown that the treatment mix is an important parameter with changing the proportion of patients on Nusinersen vs onasemogene abeparvovec the only scenario analysis that caused screening to not dominate no screening in the Velikanova et al study (13). The treatment mix in this study is not likely to represent treatment in the UK (England and Wales) as it appears that onasemogene abeparvovec was included as the treatment options for 94% of all patients in both arms of the model despite it only being licensed for use in SMA type 1 patients in Europe. Weidlich et al (14) is also the only study to include different treatment for patients with *SMN2* 4 copies. It is assumed that 56% of patients would be treated with either nusinersen or risdiplam but effectiveness rates for patients with three copies of *SMN*2 were used. While a treatment mix may be the most appropriate scenario for the basecase analysis a number of comparisons between treatments is also needed as two of the treatments, nusinersen and risdiplam, are only approved under managed access agreements in England and Wales and may not therefore represent standard care.

All the models include the country specific list price of the three treatments. However, in the UK the three treatments have commercial agreements which makes them available to the NHS at a commercial in confidence discount. Including the discounted prices may reduce the cost saving impact of screening depending on how treatment is modelled. In the Weidlich et al study (14) the cost saved through drug acquisition and administration made up 60% of the total cost saving through NBS. Weidlich et al (14) do not report if treatment costs were included in any of their sensitivity analyses. The costs of treatments are likely to have an impact on the results, in the Shih et al study (12), the cost of the treatments had 1st and 3rd biggest impact on the 1-way sensitivity analyses they conducted.

The utilities were based on those used and accepted in the NICE appraisals in two of the studies (13,14). However, the valued used come from several different sources, including the use of a clinical expert(s) for the sitting health state and they differ substantially from the values used by Shih et al (12) (see Table 5) which were based on reported values from SMA patients and carers. There are now small studies of utility values in patients who have been screened (20) which was included in one of the conference abstract models (1). Studies from SMA patients, using a consistent approach, are preferable to using utility values from a number of sources including expert opinion.

The health state costs used in two of the studies were based on a UK health utilisation survey conducted with clinicians and was accepted in the NICE appraisals of onasemogene abeparvovec. However, the evidence review group that assess the submission were concerned that the costing methods used were overly complex and conducted a sensitivity analysis excluding the social care cost component of the total cost (24,27). The costs are also based on a survey of clinicians rather than being derived by patient resource use.

Quality appraisal

Table 33 and Table 34 in Appendix 3 outline the quality appraisal of each study using the Philips checklist (7). Limited data was reported for the conference abstracts. Of the four full studies, most of them reported detail on the model structure, although not all assumption made were fully justified. The quality of the data reporting and justification varied between studies and most studies did not fully capture all forms of uncertainty.

Summary of Findings Relevant to Criterion 14: Uncertain

The included studies show NBS followed by treatment with a disease modifying treatment, in particular onasemogene abeparvovec, is generally cost-effective or cost saving when compared to no NBS and treatment with disease modifying treatment. However, there are several key uncertainties that have not been fully addressed in any of the included models including the mapping of SMA phenotypes (SMA types) to SMA genotypes (number of copies of the *SMN2* gene) and issues around treatment mix in both arms of the model, treatment price, and long-term effectiveness. Furthermore, no study considered pre-symptomatic treatment through a family history in the non-screened arm of the model.

Review summary

Conclusions and implications for policy

Based on the review there is not currently sufficient evidence on the cost-effectiveness of NBS for SMA in the UK. While the results of the included models indicate that NBS is generally cost-effective or costs saving important uncertainties have not been fully addressed. These include:

- The mapping of the SMA phenotypes (SMA Types) to SMA genotypes (SMN2 copies) to ensure the population in both arms of the model have the same distribution of disease severity
- The inclusion of pre-symptomatic treatment in the non-screened arms for patients who have a family history of the disease
- More comprehensive scenarios including pairwise comparisons between all treatment options and best supportive care as well as varying the included treatment mix. Two of the three treatments are only available in England and Wales under managed access agreements and may not therefore represent standard care.
- Additional sensitivity analyses on the long-term effectiveness of the included treatments
- Clearer assumptions on the treatment of patients with 4 or more *SMN2* copies or who were screened but were symptomatic prior to treatment
- Further validation of the health state costs and quality of life values and use of the most recent studies

It is unclear the impact addressing all these uncertainties will have on the cost-effectiveness results. Therefore, further work is needed to identify the best sources of data to address these uncertainties this may involve systematic reviews, validation of existing data, or the use of expert or patient opinion. Given the number of uncertainties a new cost-effectiveness model may be needed to ensure all relevant uncertainties can be easily assessed.

Limitations

Papers were screened by a single reviewer, with a second reviewer checking 20% of the total and any uncertain papers. Data was extracted by a single reviewer.

Not all studies included a fully published paper. To ensure the most up to date evidence was captured we have included a pre-print paper that has not yet undergone peer review and conference abstracts. However, we are aware of at least one additional study that was only included as a conference abstract in this review that is in the process of submission to a journal. This study (1) has used data and costs from patients who have undergone screening and may offer further evidence.

Appendix 1 — Search strategy

Electronic databases

The search strategy included searches of the databases shown in Table 8.

Table 8: Search Strategy

Database	Platform	Searched on date	Date range of search
MEDLINE, MEDLINE in-Process, MEDLINE Daily, Epub, Ahead of Print	Ovid SP	25/11/22	1946 to November 23, 2022
Embase	Ovid SP	25/11/22	1974 to 2022 November 23
NHS EED	CRD Website	25/11/22	1994 to March 2015
EconLit	Ovid SP	25/11/22	1886 to November 17, 2022
TUFTS CEA Registry	https://cevr.tuftsmedicalcenter.org/databases/cea-registry	25/11/22	1976 to present
MATHSSCINET	American Mathematical Society	25/11/22	1800s to present

Search Terms

Search terms included combinations of free text and subject headings (Medical Subject Headings [MeSH] for MEDLINE and NHS EED, and Emtree terms for Embase, grouped into the following categories:

- disease area: spinal muscular atrophy
- study design: economic evaluations and models

Study design was searched by using the CADTH Economic Evaluations & Models search filter for MEDLINE and Embase (https://searchfilters.cadth.ca/list?q=&p=1&ps=20&topic_facet=all%20economic%20filters%20000000%7CAll%20economic%20filters). All other sources were searched for the disease area only. The search strategy was peer-reviewed by an additional information specialist using the PRESS checklist (29).

Search terms for each database are shown in Table 9 - Table 14.

Table 9: Search strategy for MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print

#	Search terms	Results
1	Economics/	27477
2	exp "Costs and Cost Analysis"/	261287
3	Economics, Nursing/	4013
4	Economics, Medical/	9231
5	Economics, Pharmaceutical/	3089
6	exp Economics, Hospital/	25651
7	Economics, Dental/	1920
8	exp "Fees and Charges"/	31251
9	exp Budgets/	14055
10	budget*.ti,ab,kf.	34607
11	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	269751
12	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	360670
13	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	199019
14	(value adj2 (money or monetary)).ti,ab,kf.	2901
15	exp models, economic/	16160
16	economic model*.ab,kf.	4012
17	markov chains/	15846
18	markov.ti,ab,kf.	27669
19	monte carlo method/	31731
20	monte carlo.ti,ab,kf.	57770
21	exp Decision Theory/	12983
22	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	34277
23	or/1-22	860665
24	exp "Spinal Muscular Atrophies of Childhood"/	1636
25	exp Muscular Atrophy, Spinal/	6196
26	(werdnig-hoffman or werdnig hoffman).tw.	77
27	(kugelberg-welander or kugelberg welander).tw.	192
28	spinal muscular atroph*.tw.	6165
29	or/24-28	8447
30	23 and 29	160

Table 10: Search strategy for Embase (searched via Ovid)

#	Search terms	Results
1	Economics/	27477
2	Cost/	50975
3	exp Health Economics/	1651444
4	Budget/	11654
5	budget*.ti,ab,kw.	34257
6	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw.	249655
7	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	360776
8	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kw.	195672
9	(value adj2 (money or monetary)).ti,ab,kw.	2887
10	Statistical Model/	98531
11	economic model*.ab,kw.	3951
12	Probability/	59792
13	markov.ti,ab,kw.	26580
14	monte carlo method/	31731
15	monte carlo.ti,ab,kw.	56614
16	Decision Theory/	963
17	Decision Tree/	12036
18	(decision* adj2 (tree* or analy* or model*)).ti,ab,kw.	33873
19	or/1-18	2233544
20	exp hereditary spinal muscular atrophy/	0
21	spinal muscular atrophy/	4675
22	(werdnig-hoffman or werdnig hoffman).tw.	77
23	(kugelberg-welander or kugelberg welander).tw.	192
24	spinal muscular atroph*.tw.	6166
25	or/20-24	7818
26	19 and 25	258

Table 11: Search strategy for NHS EED (searched via https://www.crd.york.ac.uk/CRDWeb/HomePage.asp)

#	Search terms	Results
1	(MeSH DESCRIPTOR Spinal Muscular Atrophies of Childhood EXPLODE ALL TREES) IN NHSEED	1
2	MeSH DESCRIPTOR Muscular Atrophy, Spinal EXPLODE ALL TREES IN NHSEED	1
3	(werdnig-hoffman or werdnig hoffman) IN NHSEED	0
4	(kugelberg-welander or kugelberg welander) IN NHSEED	0
5	(spinal muscular atroph*) IN NHSEED	1
6	#1 OR #2 OR #3 OR #4 OR #5	1

Table 12: Search strategy for EconLit (searched via Ovid)

#	Search terms	Results
1	spinal muscular atroph*.mp.	1
2	(werdnig-hoffman or werdnig hoffman).mp.	0
3	(kugelberg-welander or kugelberg welander).mp.	0
4	1 or 2 or 3	1

Table 13: Search strategy for TUFTS CEA Registry (searched via https://cevr.tuftsmedicalcenter.org/databases/cea-registry)

Search Field	Search terms	Results
Keyword Is	spinal muscular atrophy	
OR Keyword Is	werdnig-hoffman or werdnig hoffman	
OR Keyword Is	kugelberg-welander or kugelberg welander	7

Table 14: Search strategy for MATHSCINET

Search Field	Search terms	Results
Anywhere	spinal muscular atrophy* or	
Anywhere	werdnig-hoffman or werdnig hoffman or	
Anywhere	kugelberg-welander or kugelberg welander	1

Results were imported into Endnote and duplicates removed.

Appendix 2 — Included and excluded studies

PRISMA flowchart

Figure 1 summarises the volume of publications included and excluded at each stage of the review. Thirteen publications were ultimately judged to be relevant to one or more review questions and were considered for extraction. Publications that were included or excluded after the review of full-text articles are detailed below.

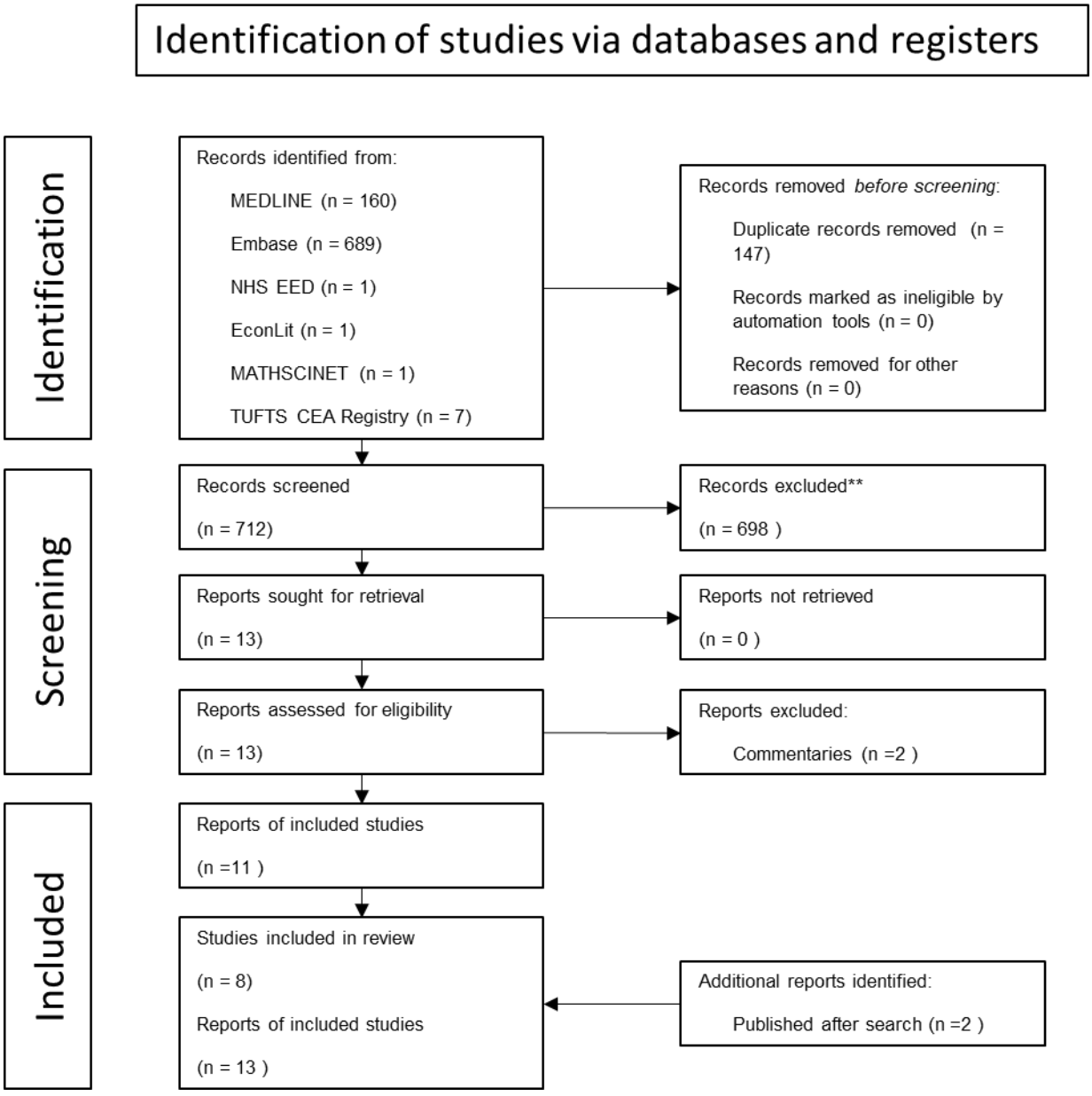

Figure 1: Summary of publications included and excluded at each stage of the review

Publications included after review of full-text articles

The 13 publications included after review of full-texts and the two additional reports identified are summarised in Table 15 below.

Publications not selected for extraction and data synthesis are clearly detailed in Table 16 below.

Table 15: Summary of publications included after review of full-text articles,

Study	Reference	Identified in search
1	Arjunji R, Zhou J, Patel A, Edwards ML, Harvey M, Wu E, et al. PND5 Cost-Effectiveness Analysis of Newborn Screening for Spinal Muscular Atrophy in the United States. Value Health Reg Issues. 2020 Sep;22(Supplement):S75.	Yes
1	Arjunji R, Zhou J, Patel A, Edwards ML, Harvey M, Wu E, et al. Cost-effectiveness analysis of newborn screening for spinal muscular atrophy (SMA) in the United States. Orphanet J Rare Dis Conf 10th Eur Conf Rare Dis Orphan Prod ECRD. 2020;15(SUPPL).	Yes
1	Arjunji R, Zhou J, Patel A, Edwards ML, Harvey M, Soverino M, et al. Pmu30 Cost-Effectiveness Analysis of Newborn Screening for Spinal Muscular Atrophy (Sma) in the United States. Value Health. 2020 May;23(Supplement 1):S238.	Yes
2	Chen HF, Hutton DW, Lavieri MS, Prosser LA. Cc2 Cost-Effectiveness Analysis of Newborn Screening and Treatment for Spinal Muscular Atrophy. Value Health. 2020 May;23(Supplement 1):S2.	Yes
3	Dangouloff T, Thokala P, Deconinck N, D'Amico A, Daron A, Delstanche S, et al. Health Economic Consideration of Newborn Screening of SMA. J Neuromuscul Dis. 2022;9(Supplement 1):S72.	Yes
3	Dangouloff T, Hiligsmann M, Deconinck N, D'Amico A, Seferian AM, Boemer F, et al. Financial cost and quality of life of patients with spinal muscular atrophy identified by symptoms or newborn screening. Dev Med Child Neurol. 2022 Jun;08:08.	Yes
4	Ghetti G, Mennini F, Marcellusi A, Bischof M, Pistillo G, Pane M. PCR145 Cost-Effectiveness Analysis of Newborn Screening for Spinal Muscular Atrophy (SMA) in Italy. Value Health. 2022 Dec 1;25(12):S419.	No
5	Jalali A, Rothwell E, Botkin JR, Anderson RA, Butterfield RJ, Nelson RE. Cost-Effectiveness of Nusinersen and Universal Newborn Screening for Spinal Muscular Atrophy. J Pediatr. 12AD;227:274-280.e2.	Yes
6	Shih ST, Farrar MA, Wiley V, Chambers G. Newborn screening for spinal muscular atrophy with disease-modifying therapies: a cost-effectiveness analysis. J Neurol Neurosurg Psychiatry. 12AD;92(12):1296–304.	Yes
6	Shih STF, Keller E, Wiley V, Farrar MA, Wong M, Chambers GM. Modelling the Cost-Effectiveness and Budget Impact of a Newborn Screening Program for Spinal Muscular Atrophy and Severe Combined Immunodeficiency. Int J Neonatal Screen. 2022 Jul 20;8(3):20.	Yes
7	Velikanova R, van der Schans S, Bischof M, van Olden RW, Postma M, Boersma C. Cost-Effectiveness of Newborn Screening for Spinal Muscular Atrophy in The Netherlands. Value Health. 10AD;25(10):1696–704.	Yes

8	Weidlich D, Servais L, Kausar I, Howells R, Bischof M. Cost Effectiveness of Newborn Screening for Spinal Muscular Atrophy in England. medRxiv. 2023 Jan 1;2023.02.09.23285715.	No

Publications excluded after review of full text articles

Of the 14 publications included after the review of titles and abstracts, two were ultimately judged not to be relevant to this review. These publications, along with reasons for exclusion, are listed in Table 16

Table 16: Publications excluded after review of full text articles

Reference	Reason for exclusion
Landfeldt E. The cost-effectiveness of newborn screening for spinal muscular atrophy. Dev Med Child Neurol. 2023 Jan;65(1):8-9. doi: 10.1111/dmcn.15314. Epub 2022 Jun 14. PMID: 35698880.	Commentary
Gillingwater TH. Maximising returns: combining newborn screening with gene therapy for spinal muscular atrophy. J Neurol Neurosurg Psychiatry. 2021 Dec;92(12):1252. doi: 10.1136/jnnp-2021-327459. Epub 2021 Jul 28. PMID: 34321342.	Commentary

Appendix 3 — Summary and appraisal of individual studies

Data Extraction

Table 17 - Table 24 includes the data extraction for the model overviews for all included studies.

Table 25 - Table 32 includes the data extraction for the model parameters and data sources for all included studies

Table 17: Model Overview for Arjunii et al

Arjunji et al	**2020, 2020, 2020 (Conference abstracts)**(15–17)	**Cost-effectiveness analysis of newborn screening for spinal muscular atrophy (SMA) in the United States**
Model Section		**Description**
Decision Problem	**Population**	10,000 newborns
	Interventions; type of screening and treatment	Screening to detect SMN1 deletions and *SMN2* copies and treatment for any positive SMA test
	Comparators: No NBS (a) Novel treatments (b) BSC, Cascade screening (a) Novel treatment (b) BSC	Symptomatic treatment with onasemnogene abeparvovec for SMA type 1
	Outcomes	Total costs, QALYs, and ICERs
	Setting	United States
Methods	**Model type**	Decision analytic model
	Model structure	Not reported
	Perspective	Third party payer perspective
	Time horizon	Lifetime horizon

	Discount rate	Not reported
	Cycle length	Not reported
	Assessment of uncertainty	Scenario and sensitivity analyses
	Key assumptions	Not reported
Results and limitations	**Main results and sensitivity analyses**	NBS and treatment for SMA up to 3 *SMN2* copies dominates no screening and symptomatic treatment. NBS and treatment for all *SMN2* copies results in an ICER of $57,969. Total costs were $2,628,116, $3,150,087, $ 2,485,813 in the no screening, NBS and treatment for all, NBS and treatment for SMA with ≤3 *SMN2* gene copies respectively. Total QALYs were 269,988, 269.997, and 269,996 respectively
	Key limitations	Only includes treatment with onasemnogene abeparvovec. Unclear how the mapping between the SMA genotypes and phenotypes is used.

BSC – Best supportive care; ICER – Incremental cost effectiveness ratio; NBS – Newborn Screening; SMA – Spinal muscular atrophy; QALYs – Quality adjusted life years;

Table 18: Model Overview for Chen et al

Chen et al	**2020 (Conference abstract)** (18)	**Cost-effectiveness analysis of newborn screening and treatment for spinal muscular atrophy**
Model Section		**Description**
Decision Problem	**Population**	Newborns (4,000,000)
	Interventions; type of screening and treatment	Newborn screening and treatment (drug or gene therapy)
	Comparators: No NBS (a) Novel treatments (b) BSC, Cascade screening (a) Novel treatment (b) BSC	Standard care, drug,
	Outcomes	Costs, QALYs, ICER
	Setting	United States
Methods	**Model type**	Decision analytic model
	Model structure	State transition model
	Perspective	Health care sector perspective
	Time horizon	Lifetime
	Discount rate	3%
	Cycle length	Not reported
	Assessment of uncertainty	Not reported
	Key assumptions	Not reported
Results and limitations	**Main results and sensitivity analyses**	NBS strategies had higher costs and QALYs than no screening. The lowest ICER was for screening and gene therapy at $187,650 compared to no screening and drug treatment. NBS and drug had an ICER of $2,694,167 when compared to no screening and standard care. And no screening drug had an ICER of $515,555 compared to NBS and drug
	Key limitations	Not reported

BSC– Best supportive care; ICER – Incremental cost effectiveness ratio; NBS– Newborn Screening; SMA– Spinal muscular atrophy; QALYs – Quality adjusted life years;

Table 19: Model Overview for Dangalouff et al

Dangouloff et al	**2022 (Conference abstract)** (1)	**Cost-effectiveness of spinal muscular atrophy newborn screening in Belgium & Health economic consideration of newborn screening for SMA**
Model Section		**Description**
Decision Problem	**Population**	Newborns in Belgium
	Interventions; type of screening and treatment	Newborn screening – with one of three available treatments
	Comparators: No NBS (a) Novel treatments (b) BSC, Cascade screening (a) Novel treatment (b) B SC	Disease modifying treatments without NBS
	Outcomes	Costs and QALYs
	Setting	Belgium
Methods	**Model type**	Decision analysis model
	Model structure	Markov model
	Perspective	Payer (Societal including costs and caregiver including loss of work and quality of life included as a sensitivity analysis)
	Time horizon	Lifetime
	Discount rate	Not Reported
	Cycle length	Not Reported
	Assessment of uncertainty	PSA and deterministic sensitivity analysis
	Key assumptions	Not reported

Results and limitations	**Main results and sensitivity analyses**	An ICER of €5,820 per QALY when only medical costs included. Including the parental choice of treatment and the global cost NBS results in a gain per patient of 20 QALYs and a reduction in costs of €2,765,172
	Key limitations	Not reported

BSC– Best supportive care; ICER – Incremental cost effectiveness ratio; NBS– Newborn Screening; PSA – Probabilistic sensitivity analysis; SMA– Spinal muscular atrophy; QALYs – Quality adjusted life years;

Table 20: Model Overview for Ghetti et al

Ghetti et al	**2022 (Conference abstract)** (19)	**Cost-effectiveness analysis of newborn screening for spinal muscular atrophy in Italy**
Model Section		**Description**
Decision Problem	**Population**	Newborns in Italy (400,000)
	Interventions; type of screening and treatment	Newborn screening – treatment included are not reported
	Comparators: No NBS (a) Novel treatments (b) BSC, Cascade screening (a) Novel treatment (b) B SC	Not Reported
	Outcomes	Costs, QALYs and Life years
	Setting	Italy
Methods	**Model type**	Decision analysis model
	Model structure	Not reported
	Perspective	Payer - National Health Service (SSN)
	Time horizon	Lifetime
	Discount rate	3%
	Cycle length	Not Reported
	Assessment of uncertainty	PSA
	Key assumptions	Higher functional health states associated with increased survival, higher utility values, and lower costs.
Results and limitations	**Main results and sensitivity analyses**	NBS is associated with 318 and 386 incremental life years and QALYs respectively. And a reduction in costs of -€143,167. NBS has a 100% probability of being cost-effective assuming a willingness to pay of €40,000 per QALY
	Key limitations	Not reported

BSC– Best supportive care; ICER – Incremental cost effectiveness ratio; NBS– Newborn Screening; PSA – Probabilistic sensitivity analysis; SMA– Spinal muscular atrophy; QALYs – Quality adjusted life years;

Table 21: Model Overview for Jalali et al

Jalali et al	**2020** (10)	**Cost-effectiveness of nusinersen and universal newborn screening for spinal muscular atrophy**
Model Section		**Description**
Decision Problem	**Population**	All newborns screened - SMA type 1
	Interventions; type of screening and treatment	Nusinersen and screening
	Comparators: No NBS (a) Novel treatments (b) BSC, Cascade screening (a) Novel treatment (b) BSC	Nusinersen no screening, standard care screening, standard care no screening
	Outcomes	Discounted event-free life years saved and discounted costs per infant. Event defined as the need for PVA. QALYs included for those over 18 years
	Setting	USA
Methods	**Model type**	Decision analytic
	Model structure	Markov Model
	Perspective	Societal perspective- direct medical costs and indirect work-related income loss of a caregiver
	Time horizon	Lifetime
	Discount rate	3% for costs and outcomes (event free life years)
	Cycle length	1 month until 30 months
	Assessment of uncertainty	Threshold analysis on price of Nusinersen, early and late treatment adjustment, PSA
	Key assumptions	Life expectancy post 30 months based at health state at 30 months. Non screened SMA diagnosed at 6 months. Treatment stops when moved to PVA health states. Screen positive patients were confirmed for type 1 SMA before treatment initiation.

Results and limitations	**Main results and sensitivity analyses**	The ICER for NBS & treatment compared to no screening and no treatment was $330,558 per event free LY saved. The ICER for NBS & treatment compared to no screening and treatment was $199,510 but no screening and treatment was eliminated as an extendedly dominated strategy. The ICER was reduced with a lower treatment price and by using the data from the NURTURE trial.
	Key limitations	Only includes nusinersen and type 1 SMA. Doesn't base screen results on *SMN2* copies. Doesn’t include any pre-symptomatic treatment in the non-screen arm.

BSC – Best supportive care; ICER – Incremental cost effectiveness ratio; NBS – Newborn Screening; PSA – Probabilistic sensitivity analysis; PVA – Permanent ventilator assistance; SMA – Spinal muscular atrophy; QALYs – Quality adjusted life years;

Table 22: Model Overview for Shih et al

Shih et al	**2021**(12)	**Newborn screening for spinal muscular atrophy with disease-modifying therapies: a cost-effectiveness analysis**
Model Section		**Description**
Decision Problem	**Population**	Infants in the Australian newborn screening programme
	Interventions; type of screening and treatment	Screening and early treatment with nusinersen or gene therapy
	Comparators: No NBS (a) Novel treatments (b) BSC, Cascade screening (a) Novel treatment (b) BSC	Nusinersen, gene therapy or supportive care
	Outcomes	Costs and QALYs
	Setting	Australia
Methods	**Model type**	Decision analytic model
	Model structure	Decision tree followed by markov model with 11 health states
	Perspective	Societal perspective – included informal care and parents' loss of productivity as well as direct medical costs
	Time horizon	5 and 60 years
	Discount rate	3% per year costs and QALYs
	Cycle length	6 months
	Assessment of uncertainty	One-way sensitivity analysis, PSA, and scenario analysis on costs of nusinersen and gene therapy
	Key assumptions	If false negative assume symptomatic treatment outcomes. Assumed same effectiveness for gene therapy and pre-symptomatic nusinersen. All patients start in non-sitter health state. Patients can lose a milestone and would stay in the regressed health state until death. Only those in the non-sitter health state could transition to permanent ventilation health state.

Results and limitations	**Main results and sensitivity analyses**	Dominant if compare gene therapy to late nusinersen over a 60 year horizon., ICER ranging from dominated to $216.000 to $706,000 for other scenarios at 60 years. At five years NBS and nusinersen dominated NBS and gene therapy. Other strategies ranged from $494,000 to $1,360,000. Most sensitive parameters include the cost of nusinersen maintenance injection, SMA incidence, the cost of gene therapy, discount rate, utility values of independent walker.
	Key limitations	Does not include no NBS and pre-symptomatic treatment. Does not include a mix of treatments, treatment with risdiplam, or gene therapy specific transition rates. No mapping between the SMA genotypes and phenotypes. Does not include symptomatic treatment in the NBS arm

ICER – Incremental cost effectiveness ratio; NBS – Newborn Screening; PSA – Probabilistic sensitivity analysis; SMA – Spinal muscular atrophy; QALYs – Quality adjusted life years;

Table 23: Model Overview for Velikanova et al

Velikanova et al	**2022**(13)	**Cost-effectiveness of newborn screening for spinal muscular atrophy in the Netherlands**
Model Section		**Description**
Decision Problem	**Population**	Infants in the Dutch newborn bloodspot screening programme (169,680)
	Interventions; type of screening and treatment	A real-time polymerase chain reaction genotyping assay for *SMN1*
	Comparators: No NBS (a) Novel treatments (b) BSC, Cascade screening (a) Novel treatment (b) BSC	No NBS and novel treatments - nusinersen and onasemnogene abeparvovec
	Outcomes	QALYs and costs
	Setting	Netherlands
Methods	**Model type**	Cost utility model
	Model structure	Decision tree followed by a markov model with 6 health states
	Perspective	Payer perspective in base case (Societal in a sensitivity analysis)
	Time horizon	Lifetime
	Discount rate	4% costs 1.5% health outcomes
	Cycle length	6 months first 3 years and 12 months thereafter
	Assessment of uncertainty	Deterministic sensitivity analysis, PSA, scenario analysis including discount rate, time horizon, analysis perspective, incidence, treatment percentage, costs for NBS, and percentage *SMN1* deletion.

	Key assumptions	Patients with SMN1 point mutations are not identified via screening. Motor milestones achieved at the end of follow-up in the clinical trials were sustained until death. All patients with SMA type 1 or NBS detected patients start in the not sitting health state. SMA types 2 and 3 start the model in sitting or walking respectively. 94% of patients are treated with OA and 6% with nusinersen in both arms of the model
Results and limitations	**Main results and sensitivity analyses**	NBS reduces costs and increases QALYs with an ICER of -€37,564. The PSA indicated that NBS has a 100% probability of being cost saving. Per SMA patient NBS increases the number of QALYs by 19 and reduces the costs €708,095. Treatment costs are higher in the screened arm. The only scenario with a positive ICER is increasing the proportion of patients on nusinersen.
	Key limitations	Onasemnogene abeparvovec is included as treatment for all SMA patients. Unclear if this includes SMA types 2 and 3 in the non-screened arm which is outside of the license. Does not include treatment with risdiplam. Limited number of transitions to a worse health state were allowed. Does not include pre-symptomatic treatment in the non-screened arm. No mapping between the SMA genotypes and phenotypes. Does not include symptomatic treatment in the NBS arm. Limited data presented on the transition probabilities and treatment effectiveness.

ICER – Incremental cost effectiveness ratio; NBS – Newborn Screening; OA – onasemnogene abeparvovec; PSA – Probabilistic sensitivity analysis; SMA – Spinal muscular atrophy; QALYs – Quality adjusted life years;

Table 24: Model Overview for Weidlich et al

Weidlich et al	**2023 (Pre-Print)** (14)	**Cost-effectiveness of newborn screening for spinal muscular atrophy in England and Wales**
Model Section		**Description**
Decision Problem	**Population**	Newborns in England and Wales (585,195)
	Interventions; type of screening and treatment	Screening for 5q SMA
	Comparators: No NBS (a) Novel treatments (b) BSC, Cascade screening (a) Novel treatment (b) BSC	No NBS and novel treatments (Onasemnogene abeparvovec, nusinersen, risdiplam, and best supporting care.
	Outcomes	Costs, QALYs, and Life years (Lys)
	Setting	England and Wales
Methods	**Model type**	Cost utility analysis
	Model structure	Decision tree followed by Markov model with 6 health states
	Perspective	Payer in base case (societal in a sensitivity analysis)
	Time horizon	Lifetime horizon
	Discount rate	3.5% for costs and QALYs
	Cycle length	6 months for 3 years and 1 year afterwards
	Assessment of uncertainty	DSA and PSA. Scenarios - discount rate, time horizon, perspective, and survival
	Key assumptions	SMA 1 treated within 6 month, SMA 2 within 18 months, SMA 3 withing 4 years. Pre-symptomatic infants with four copies of *SMN2* efficacy data for patients with three *SMN2* copies were applied. 40% of patients with two copies of *SMN2* are assumed to become symptomatic by the time they receive treatment. 4% of patients with SMA are assumed to have an SMN1 point mutation and are thus not detected by qPCR-based newborn screening. Treated patients cannot regress. Not all patients identified by NBS will be asymptomatic at treatment. Treatment mix based on clinical input and differs between the NBS arm and the non-screened arm.

Results and limitations	**Main results and sensitivity analyses**	NBS is cost saving and increases QALYs compared to no screening. The ICER is -£117,541. Both treatment and healthcare costs are lower in the NBS arm. The PSA indicates that there is a 100% probability of NBS being cost-effective at a threshold of £20,000 or £30,000 per QALY.
	Key limitations	Assumes no patients currently identified and treated pre-symptomatically. No mapping between the SMA genotypes and phenotypes. Limited data presented on the transition probabilities and treatment effectiveness. Limited sensitivity and scenario analyses on key assumptions and parameters.

DSA – Deterministic sensitivity analysis; ICER – Incremental cost effectiveness ratio; NBS– Newborn Screening; PSA – Probabilistic sensitivity analysis; QALYs – Quality adjusted life years; qPCR – Quantitative polymerase chain reaction

Table 25: Model Parameters and data sources Arjunji et al

Arjunji et al		**2020, 2020, 2020 (Conference abstracts)** (15–17)	**Cost-effectiveness analysis of newborn screening for spinal muscular atrophy (SMA) in the United States**	
Parameter		**Parameter value(s)**	**Description of parameter(s) and evidence used**	**Source**
Epidemiology	**Incidence**	9.4 per 100,000		Lally et al 2017(30)
	SMN1 deletion	95%/5%	*SMN1* deletion/*SMN1* point mutation	Kraszewski et al 2018 (31), Chien et al 2018 (5)
SMA phenotype and genotype breakdown	***SMN2* copies and conditional SMA type distribution**			
	***SMN2* - 2 copies**	45%		Vill et al 2019 (32), Calucho et al 2018 (33)
	(SMA Type I/II/III)	78.88%/16.48%/4.64%		
	***SMN2* - 3 copies**	19%		
	(SMA Type I/II/III)	(14.74%/54.27%/30.99%)		
	***SMN2* - 4 copies**	36%		
	(SMA Type I/II/III)	0.58%/11.41%/88.01%)		
	SMA type distribution- undetected SMA or *SMN1* point mutation			
	(SMA Type I/II/III)	58.00%/29.00%/13.00%		
Screening	**Type of screening test**			
	Screening test accuracy	Not reported		

	Resource use and costs	$10, $20	Cost of the screening test and reflect screening (per newborn with SMA-positive results from initial screening)	Assumption
Modelling of the disease	**Health states**	Not reported		
	Transitions/progression rates	Not reported		
	Resource use and cost	Not reported		Institute for clinical and economic review report (34)
Treatment	**Resource use and costs (if not included above)**	$2,125,000, $141, $125	Onasemnogene abeparvovec drug cost, symptomatic administration, pre-symptomatic administration	Red book 2019 (35), CMS physician fee schedule 2018 (36)
	Treatment effect (if not included above)	Not reported		
Health related quality of life and life years	**Health related quality of life**	Not reported		Institute for clinical and economic review report (34)
	Life years	Not reported		

SMA – Spinal muscular atrophy

Table 26: Model Parameters and data sources Chen et al

Chen et al		**2020 (Conference abstact)** (18)	**Cost-effectiveness analysis of newborn screening and treatment for spinal muscular atrophy**	
Parameter		**Parameter value(s)**	**Description of parameter(s) and evidence used**	**Source**
Epidemiology	**Incidence**	Not reported		
	SMA phenotype and genotype breakdown	Not reported		
Screening	**Type of screening test**	Not reported		
	Screening test accuracy	Not reported		
	Resource use and costs	Not reported		
Modelling of the disease	**Health states**	Not reported		
	Transitions/progression rates	Not reported		
	Resource use and cost	Not reported		
Treatment	**Resource use and costs (if not included above)**	$750,000 1st year, $375,000 yearly	Nusinersen	
		$2,000,000	Onasemnogene abeparvovec	
	Treatment effect (if not included above)	Not reported		
Health related quality of life and life years	**Health related quality of life**	Not reported		

	Life years	Not reported

SMA – Spinal muscular atrophy

Table 27: Model Parameters and data sources Dangouloff et al

Dangouloff et al		**2022 (Conference abstract)** (1)	**Cost-effectiveness of spinal muscular atrophy newborn screening in Belgium & Health economic consideration of newborn screening for SMA**	
Parameter		**Parameter value(s)**	**Description of parameter(s) and evidence used**	**Source**
Epidemiology	**Incidence**	Not reported		
	SMA phenotype and genotype breakdown	Not reported		
Screening	**Type of screening test**	Not reported		
	Screening test accuracy	Not reported		
	Resource use and costs	Not reported		
Modelling of the disease	**Health states**	Not reported		
	Transitions/progression rates	Not reported		
	Resource use and cost	€50,780, €24,320, €3,250	Annual medical costs of untreated SMA patients with 2, 3, or 4 *SMN2* copies respectively	
		€30,580, €18,059 €8,045	Annual medical costs of symptomatically treated patients SMA patients with 2, 3, or 4 *SMN2* copies respectively (excluding treatment costs)	
Treatment in screened patients	**Resource use and costs (if not included above)**	€3,913, €1,807, €1,884	Annual medical costs of screened and treated SMA patients with 2, 3, or 4 *SMN2* copies respectively (excluding treatment costs)	
	Treatment effect (if not included above)	Not reported		

Health related quality of life and life years	**Health related quality of life**	Valued not reported	QALYs estimated from a study of SMA patients both diagnosed through NBS and symptomatically
	Life years	Not reported	

SMA – Spinal muscular atrophy; QALYs – Quality adjusted life years;

Table 28: Model Parameters and data sources Ghetti et al

Ghetti et al		**2022 (Conference abstract)** (19)	**Cost-effectiveness analysis of newborn screening for spinal muscular atrophy in Italy**	
Parameter		**Parameter value(s)**	**Description of parameter(s) and evidence used**	**Source**
Epidemiology	**Incidence**	Not reported		
	SMA phenotype and genotype breakdown	Not reported		
Screening	**Type of screening test**	Not reported		
	Screening test accuracy	Not reported		
	Resource use and costs	Not reported		
Modelling of the disease	**Health states**	Not reported		
	Transitions/progression rates	Not reported	NURTURE, RAINBOWFISH, SPR1NT trials	
	Resource use and cost	Not reported		
Treatment	**Resource use and costs (if not included above)**	Not reported		
	Treatment effect (if not included above)	Not reported		

Health related quality of life and life years	**Health related quality of life**	Not reported
	Life years	Not reported

SMA – Spinal muscular atrophy;

Table 29: Model Parameters and data sources Jalali et al

Jalali et al		**2020** (10)	**Cost-effectiveness of nusinersen and universal newborn screening for spinal muscular atrophy**	
Parameter		**Parameter value(s)**	**Description of parameter(s) and evidence used**	**Source**
Epidemiology	**Incidence**	9.4 per 100,000	Prevalence in the USA	Lally et al 2017(30)
	SMA phenotype and genotype breakdown	60% SMA type 1		Ogino et al 2004 (32)
Screening	**Type of screening test**		Not reported	
	Screening test accuracy		Not reported	
	Resource use and costs	$2.91 per infant	Based on the increase in the total price of the newborn screening kit in Utah following the introduction of SMA screening.	Not reported
Modelling of the disease	**Health states**		Not clearly reported. SMA-free, untreated SMA, treated SMA, motor milestone response, PVA, and death.	
	No treatment	Death 3.73%, Ventilator support 2.89%, MM response 0%,	Monthly	
	Transitions/progression rates	Death PVA 3.19; Ventilator support N 1.94%, NT 2.89%, NURTURE 0%; MM response N 5.29%, NT 0%, Death N 1.36%, NT 3.73%, NURTURE 0% - Monthly; Adjustment for early treatment 0.516, adjustment for late treatment 1.484.;MM	Non-treatment from sham control group of the ENDEAR trial. Treated patients ENDEAR trial. Additional analyses use NURTURE trial. Death from PVA not from trial	Mendell et al 2017 (ENDEAR trial) (37), Death from PVA Bartlett et al 2000 (38), De Vivo et al 2019 (NURTURE study) (39)

		response ≤13 months 17.66 >13 months 100% NURTURE		
	Resource use and cost	PVA Direct monthly costs $13,564. Indirect monthly costs $1034	Direct medical costs of PVA based on estimates from Sevick et al and uplifted. Indirect costs for caregivers from the Bureau of Labor Statistics; Employment Cost Index and Sevick et al	Sevick et al 1996 (40)
Treatment	**Resource use and costs (if not included above)**	Single dose injection $125,000	Costs of administration of nusinersen were based on private payer adjustments of Medicare's average payment and included lumbar puncture, moderate sedation <5 years, medicare to private payer rate professional fee (%),	
	Nusinersen	Death 1.36%, Ventilator support 1.94%, MM response 5.29%,	Monthly	
	Nusinersen (NURTURE)	Death 0%, Ventilator support 0%, MM response ≤13 months 17.66%, MM response >13 months 100%	Monthly	
	Treatment effect (if not included above)	Early treatment 0.516, Late treatment 1.484	Adjustment for timing of treatment	Finkel et al 2017 (41)

Health related quality of life and life years	**Health related quality of life**	71.4 normal population, 64.4 SMA w/o PVA	Used asthma as a proxy, only included for those over 18 years	Jia et al 2013 (42)
	Life years (discounted)	Normal 79.5 (29.91), SMA w/o PVA and with pre-symptomatic treatment 75 (29.48), SMA with PVA 25.3 (16.4)	Asthma used as a proxy for SMA w/o PVA, Duchenne with nocturnal ventilation used as proxy for SMA with PVA	Jia et al 2013 (42), Eagle et al 2002 (43)

MM – Motor milestone; PVA – Permanent ventilator assistance; SMA – Spinal muscular atrophy ; w/o - without

Table 30: Model Parameters and data sources Shih et al

Shih et al		**2021** (12)	**Newborn screening for spinal muscular atrophy with disease-modifying therapies: a cost-effectiveness analysis**	
Parameter		**Parameter value(s)**	**Description of parameter(s) and evidence used**	**Source**
Epidemiology	**Incidence**	0.000091		Sugarmen et al 2012 (44)
	SMA phenotype	SMA1 0.58, SMA2 0.29, SMA3 0.13		Farrar et al 2013 (45)
	SMA genotype	2 copies SMN2 0.69, 3 copies SMN2 0.31	Proportion copies from the pilot of NBS in Australia	Kariyawasam et al 2020 (46)
Screening	**Type of screening test**		A real-time polymerase chain reaction 4-plex assay assay for SMN1 on the dried blood spot to detect homozygous SMN1 deletion. A second tier screen by droplet digital PRC to measure number of *SMN2* copies in those with 0 *SMN1* copies.	Shih et al 2022 (11)
	Screening test accuracy - False negative % in screen	0.00000576	Data on screening test accuracy from the pilot of NBS in Australia	Kariyawasam et al 2020 (46)
	Screen retest due to non-amplification	0.012		Kariyawasam et al 2020 (46)
	Further test % in screen	0.0000854		Kariyawasam et al 2020 (46)
	SMA confirmation in re-test	1		Kariyawasam et al 2020 (46)

	Resource use and costs - NBS screen test cost	$5	Screening and diagnosis costs collected from the Australian pilot NBS programme.	Kariyawasam et al 2020 (46)
	Resource use and costs - Screen cost with further sample collection	$12		Kariyawasam et al 2020 (46)
Modelling of the disease	**Health states**	All start in non-sitter health state	Non-sitter, sitting w/o support, standing with assistance, walking with assistance, walking unaided, loss sitting, loss standing, loss assisted walking, loss independent walking, permanent ventilation/nutrition support, death	
	Transitions/progression rates - supportive care - SMA1	SMA1 - patients can remain in the non-sitter state or transition to nutrition support or ventilator support or death. Mortality rate of 0.29	For the supportive care arm observational studies were used.	Finkel et al 2017 (41)
	Transitions/progression rates - supportive care - SMA2	Patients can improve up to the walking with assistance health state. And they can also lose a motor milestone. Mortality rate of 0.004	For the supportive care arm observational studies were used.	Finkel et al 2014 (47), Chabanon et al 2018 (48), Farrar et al 2013 (45)
	Transitions/progression rates - supportive care - SMA3	Patients can improve up to the walking unaided health state. They can lose a motor milestone although the probability of this is small. They do not transition into the nutrition/ventilation support	For the supportive care arm observational studies were used.	Chabanon et al 2018 (48),

	health state. Background mortality is used		
Transition/progression rates nusinersen no NBS	Patients can improve up to the walking unaided health state. Patients do not lose motor milestones. They do not transition into the nutrition/ventilation support health state. Background mortality is used	ENDEAR, CHERISH and SHINE (extension to ENDEAR) were used to estimate transition probabilities for nusinersen in the no NBS arm.	Finkle et al 2017 (41), Mercuri et al 2018 (49), Finkel et al 2020 (50)
	SMA1 annual costs $231,717	Australian study of the economic burden of SMA	Chambers et al 2020 (21)
	SMA2 annual cost $152,469	Australian study of the economic burden of SMA	Chambers et al 2020 (21)
Resource use and costs SMA general	SMA3 annual costs $95966	Australian study of the economic burden of SMA	Chambers et al 2020 (21)
	Respiratory and nutritional care $10,712	From a systematic review of economic burden of spinal muscular atrophy	Dangouloff et al 2021 (51)
	Injection epidosde cost $3731, Loading cost $318,164, maintenance cost $119311, one dose cost $75810	Costs of nusinersen based on the NURTURE study treatment regimen. Four loading doses in the first 2 months followed by a maintenance dose every 4 months. For each nusinersen injection and gene therapy episode a same day admission was	De Vivo 2019 (NURTURE) (39),

			required to undertake the procedures and post injection observation. Costed using routine Australian data sources.	
	Resource use and cost	Gene therapy cost $1,540,000, Follow up cost $158, Initial year cost $4312		
	Resource use and costs (if not included above)		One of cost of gene therapy based on overseas comparable price, follow-up of 10 consultations in the first year and then biannually. Costs of nusinersen are described above.	
Treatment	**Treatment effect - transition/progression rates - nusinersen/gene therapy NBS**	Patients can improve up to the walking unaided health state. Patients do not lose motor milestones. They do not transition into the nutrition/ventilation support health state. Background mortality is used	NURTURE study for nusinersen and gene therapy in the NBS arm. No deaths or loss of motor milestones were reported. Population background mortality was used.	De Vivo 2019 (NURTURE) presymptomatic(39) , Pharmacuetical benefits scheme 2018 (52), Medicare benefit schedule book 2018 (53). National efficient price determination 2019 (54)
Health related quality of life and life years	**Health related quality of life**	0,0.02,0.11,0.25,0.38,0.64,0,0.2(%)	Non-sitter with nutrition/ventilation support, Non-sitter, sitting w/o support, standing with assistance, walking with assistance, standing/walking unaided, death, disultility % for loss of motor milestone. Values from a Australian study on the pre-nusinersen and	Chambers et al 2020 (21), Belter et al 2020 (23)

		supplemented by a US community study.
Life years	Not applicable	

NBS– Newborn Screening; SMA– Spinal muscular atrophy; QALYs – Quality adjusted life years; w/o - without

Table 31: Model Parameters and data sources Velikanova et al

Velikanova et al		**2022** (13)	**Cost-effectiveness of newborn screening for muscular atrophy in the Netherlands**	
Parameter		**Parameter value(s)**	**Description of parameter(s) and evidence used**	**Source**
Epidemiology	**Incidence**	1 in 10,000		Ogino et al 2004 (55)
	SMA phenotype	58% type 1, 29% type 2, 13% type 3		Ogino et al 2004 (55)
	SMA genotype	45% 2 copies, 33% 3 copies, 22% 4 copies	Screened - SMN1 Deletion SMN2: 2 copies, 3 copies, 4 copies.	Vill et al 2019 (32), Servais et al 2020 (56)
	Homozygous deletion	99%	Those with a heterozygote deletion (1%) will not be picked up by NBS	Heijnen et al 2020 (57)
Screening	**Type of screening test**		A real-time polymerase chain reaction genotyping assay for SMN1 on the dried blood spot to detect homozygous SMN1 deletion	
	Screening test accuracy		Only rate of homozygous deletion is reported	
	Resource use and costs	€4.95. €1,600	Cost of screening test and tariff for diagnostics for referred children	Heijnen et al 2020 (57)
Modelling of the disease	**Health states**	Broad range of normal development (BRND), Walking, Sitting, Not Sitting, Permanent assisted ventilation (PAV), and death.	Survival is based on health state and was extrapolated using Guyot method. PAV health state was based on Gergoretti et al. The NueroNEXT study was used for the not-sitting state where patients could regress to PAV as well as die. Survival for SMA type 1 patients in the sitting state was modelled from a 52-ear targeted prospective as well as a retrospective study. For the walking and	Gregoretti et al 2013 (58), Kolb et al 2017 (59), Zerres et al 1997 (60)

			BRND health states, Dutch normal life expectancy was used.	
Symptomatic diagnosis	**Transition/progression rates - OA**	Values not reported	For SMA type 1 transition probabilities were calculated with data from START and ST1VE for those treated with OA. Motor milestones achieved after 36 months (end of follow-up in clinical trials) is sustained until death.	Al-Zaidy et al 2019 (61), Day et al 2021(62)
	Transitions/progression rates – nusinersen (SMA Type 1)	Values not reported	For SMA type 1 transition probabilities were calculated with data ENDEAR and SHINE (an extension of ENDEAR) for patients treated with nusinersen. Motor milestones achieved after 24 months (end of follow-up in clinical trials) is sustained until death.	Finkel et al 2017 (41), Johnson et al 2020 (63), Castro et al 2021 (64), NICE documents (24,25)
	Transitions/progression rates – nusinersen (SMA Types 2 & 3)	Values not reported	For SMA types 2 and 3 transition probabilities were based on the CS2/CS12 clinical trial. Motor milestones achieved after 36 months OA and 24 months nusinersen (end of follow-up in clinical trials) are sustained until death.	Darras et al 2019 (65)

	Resource use and cost	€600,108 (PAV), €182,529 (not sitting), €99,656 (Sitting), €9497 (walking),	Costs were taken from the UK health care resource use study, national Health Service Prescription Costs Analysis, Dutch cost guidelines, and the Dutch Health Authority.	
Treatment (nusinersen)	**Resource use and costs (if not included above)**	€83,300 (dose), €3278 (administration costs)		Heijnen et al 2021 (57)
	Treatment effect (if not included above)	Values not reported	NURTURE study used estimate transition probabilities. Motor milestones achieved after 24 months (end of follow-up in clinical trials) is sustained until death.	De Vivo et al 2019 (39)
Treatment (OA)	**Resource use and costs (if not included above)**	€1.945,000 (dose), €3278 (administration costs)		
	Treatment effect (if not included above)	Values not reported	START and ST1VE study used estimate transition probabilities. Motor milestones achieved after 36 months (end of follow-up in clinical trials) is sustained until death.	Al-Zaidy et al 2019 (61), Day et al 2021(62)
Health related quality of life and life years	**Health related quality of life**	0.6, 0.19, 0	Sitting health state, non-sitting state, PAV health state (Dutch clinical experts). Dutch population norms were used for walking and BRND health states. Thompson et al cross-sectional study of patients with SMA in Europe. Tappenden et al derived from clinical experts who advised the ERG.	Tappenden et al 2018 (25,66), Thompson et al 2017 (22), Lin et al 2015 (67) Ara et al 2010 (68)
	Life years	Not applicable		

BRND – Broad range of normal development; ERG – Evidence review group; OA – onasemnogene abeparvovec; PVA – Permanent ventilator assistance; SMA – Spinal muscular atrophy;

Table 32: Model Parameters and data sources Weidlich et al

Weidlich et al		**2023 (Pre-Print) (14)**	**Cost-effectiveness of newborn screening for spinal muscular atrophy in England and Wales**	
Parameter		**Parameter value(s)**	**Description of parameter(s) and evidence used**	**Source**
Epidemiology	**Incidence**	1 in 10,000	5q SMA	Sugarman et al 2012 (39)2, Ogino et al 2002 (55), van der Pol 2020 (expert opinion meeting) (69)
	homozygous deletion	96%	4% of cases have a point mutation in SMN1 and are not detected through NBS	Alas et al 2009 (70)
	SMA phenotypes	58% type 1, 29% type 2, 13% type 3	Distribution of patients identified by NBS and symptomatic at time of treatment. Unclear what distributions are used in the no screen arm of the model.	Ogino et al 2004 (55)
	SMA genotypes	46.7% two copies, 25% three copies, and 28.3% four copies.	SMN2 copies distribution based on literature from screening pilots and programmes. 40% of patients with SMN2 two copies assumed to become symptomatic by the time they receive treatment.	Vill et al 2019 (32), Boemer et al 2021(71), Dangouloff et al 2023 (20), Chien et al 2017 (5), Hale et al 2021 (72), Kariyawasam et al 2020 (46), Kay et al 2020 (73), Vill et al 2021 (28)
Screening	**Type of screening test**		qPCR-based newborn screening	

	Screening test accuracy			
	Resource use and costs	£4.54 heel prick test. £1,200 confirmatory genetic test	Based on Dutch value. Prices from Oxford Genetic Laboratories assuming both gene sequencing and multiplex ligation-dependent probe amplification are needed.	
Modelling of the disease	**Health states**	Broad range of normal development (BRND), Walking, sitting, not sitting, PVA, and death	Heath state entered depends on the method of diagnosis. Survival is based on health state and was extrapolated using Guyot method. PAV health state was based on Gergoretti et al. The NueroNEXT study was used for the not-sitting state where patients could regress to PAV as well as die. Survival for SMA type 1 patients in the sitting state was modelled from a 52-ear targeted prospective as well as a retrospective study. For the walking and BRND health states, Dutch normal life expectancy was used.	Gregoretti et al 2013 (58), Kolb et al 2017 (59), Zerres et al 1997 (60)
	Transitions/progression rates		For untreated patients 24% SMA type 1 would lose ability to sit between 0.7 and 29.1 years, 9% of patients SMA type 3 could lose ability to sit between 15.5 and 40.4 years. 51% of SMA type 3 would lose the ability to walk between 2.5 and 65.7 years based on a natural history study of S MA - used in HTA submissions	Wadman et al 2018 (74)
	OA	Values not reported	Pooled data from the START, STR1VE-US and STR1VE-EU studies are used for the first three years of the model for symptomatically detected patients with	

			Type 1 SMA. Data from CS2/CS12 is used for Type 2 and Type 3.	
	Nusinersen	Values not reported	Data from the SHINE study was used for the first three years of the model for symptomatically detected patients with Type 1 SMA. Data from CS2/CS12 was used for Type 2 and Type 3.	
	Risdiplam	Values not reported	Data from the FIREFISH Part 1 and part 2 studies were used for the first three years of the model for symptomatically detected patients with Type 1 SMA. Data from CS2/CS12 was used for Type 2 and Type 3.	
Treatment proportions	**Type 1**	56% OA, 2% Nusinersen, 22% Risdiplam, 20% BSC	Based on expert opinion	
	Type 2	0% OA, 10% Nusinersen, 90% Risdiplam, 0% BSC	Based on expert opinion	
	Type 3	0% OA, 10% Nusinersen, 90% Risdiplam, 0% BSC	Based on expert opinion	
	Resource use and cost	£283,710 (PAV), £112,500 (not sitting), £67,567 (Sitting), £8,333 (walking), £414 (BRND)	Costs based on a UK health care resource utilization study and uplifted and assumption of two neurologist visits per year for BRND	Unclear
Treatment	**Resource use and costs (if not included above)**	Values not reported	Treatment and administration costs were based on the UK list prices and the latest National Health Service (NHS) reference costs (2019/2020). But values are not reported.	

Transition probabilities	**No treatment**	Values not reported	Long term efficacy. PAV - Gregoretti et al 2013, Not sitting Kolb SJ et al 2017, Sitting Zerres et al 1997, walking and BRND general population life expectancy.	Gregoretti et al 2013 (58), Kolb et al 2017 (59), Zerres et al 1997 (60)
	OA	Values not reported	Data from the SPR1NT study is used for the first three years of the model for pre-symptomatically detected patients with two, three, and four copies of SMN2. Data for patients with four copies is extrapolated from data with three copies.	
	Nusinersen	Values not reported	Data from the NURTURE study is used for the first three years of the model for pre-symptomatically detected patients with two, three, and four copies of SMN2. Data for patients with four copies is extrapolated from data with three copies.	
	Risdiplam	Values not reported	Data from the RAINBOWFISH study is used for the first three years of the model for pre-symptomatically detected patients with two, three, and four copies of SMN2. Data for patients with four copies is extrapolated from data with >2 copies	
	Patients identified via NBS but treated symptomatically	Values not reported	Data from CS2/CS12 (all treatments) for SMA type 3 was used as a proxy based on clinical input.	
Treatment proportions	***SMN2* two copies**	93% OA, 6% Nusinersen, 0% Risdiplam, 1% BSC	Based on expert opinion	
	***SMN2* three copies**	93% OA, 6% Nusinersen, 0% Risdiplam, 1% BSC	Based on expert opinion	
	***SMN2* four copies**	0% OA, 6% Nusinersen, 50% Risdiplam, 44% BSC	Based on expert opinion	

	***SMN2* two copies (identified via NBS but treated symptomatically)**	93% OA, 6% Nusinersen, 0% Risdiplam, 1% BSC	Based on expert opinion	
	Treatment effect (if not included above)			
Health related quality of life and life years	**Health related quality of life**	0 (PVA), 0.19 (not sitting), 0.6 (sitting), General population (walks and BRND)	Preferred values from NICE appraisal of onasemnogene abeparvovec and Institute for clinical and economic review	Clinical experts (PVA), Thompson et al 2017 (not sitting) (22), Tappenden et al 2018 (sitting) (25,66), Ara and Brazier 2010 (Walking and BRND) (68)
	Life years	Not applicable		

BRND – Broad range of normal development; NBS– Newborn Screening; OA – onasemnogene abeparvovec; PVA – Permanent ventilator assistance; qPCR – Quantitative polymerase chain reaction PVA – Permanent ventilator assistance

Appraisal for quality and risk of bias

Quality assessments of included studies are reported below. Table 33 includes those studies where only a conference abstract was available. Table 34 includes studies where a full paper was available.

Table 33: Philips checklist for Conference Abstracts

		Response by study			
Quality Criteria	Question(s) for critical appraisal	Arjunji et al (15–17)	Chen et al (18)	Dangouloff et al (20)	Ghetti et al (19)
STRUCTURE (S)					
S1	Is there a clear statement of the decision problem?	Yes	Yes	Yes	Yes
	Is the objective of the evaluation and model specified and consistent with the stated decision problem?	Yes	Yes	Yes	Yes
	Is the primary decision maker specified?	No	No	No	No
S2	Is the perspective of the model stated clearly?	Partly	Yes	Yes	No
	Are the model inputs consistent with the stated perspective?	Yes	Unclear	Unclear	Unclear
	Has the scope of the model been stated and justified?	Partly	Partly	Partly	Partly
	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Yes	Yes	Yes	Yes
S3	Has the evidence regarding the model structure been described? Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	No	No	No	No
	Are the sources of data used to develop the structure of the model specified?	Partly	No	No	No
	Are the causal relationships described by the model structure justified appropriately?	Unclear	No	No	Unclear
S4	Are the structural assumptions transparent and justified?	Unclear	Unclear	Unclear	Unclear

	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Unclear	Unclear	Unclear	Unclear
S5	Is there a clear definition of the options under evaluation?	Partly	Yes	Partly	No
	Have all feasible and practical options been evaluated?	No	Partly	Partly	Unclear
	Is there justification for the exclusion of feasible options?	No	No	No	No
S6	Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	Unclear	Yes	Yes	Partly
S7	Is the time horizon of the model sufficient to reflect all important differences between options?	Yes	Yes	Yes	Yes
	Is the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?	No	No	No	No
S8	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?	Unclear	Unclear	Unclear	Unclear
S9	Is the cycle length defined and justified in terms of the natural history of disease?	No	No	No	No
DATA (D)					
D1	Are the data identification methods transparent and appropriate given the objectives of the model?	Unclear	Unclear	Unclear	Unclear
	Where choices have been made between data sources, are these justified appropriately?	Unclear	Unclear	Unclear	Unclear
	Has particular attention been paid to identifying data for the important parameters in the model?	Unclear	Unclear	Unclear	Unclear
	Has the process of selecting key parameters been justified and systematic methods used to identify the most appropriate data?	Unclear	Unclear	Unclear	Unclear
	Has the quality of the data been assessed appropriately?	Unclear	Unclear	Unclear	Unclear
	Where expert opinion has been used, are the methods described and justified?	Unclear	Unclear	Unclear	Unclear
D2	Is the pre-model data analysis methodology based on justifiable statistical and epidemiological techniques?	Unclear	Unclear	Unclear	Unclear

D2a	Is the choice of baseline data described and justified?	No	No	No	No
	Are transition probabilities calculated appropriately?	Unclear	Unclear	Unclear	Unclear
	Has a half cycle correction been applied to both cost and outcome?	Unclear	Unclear	Unclear	Unclear
	If not, has this omission been justified?	No	No	No	No
D2b	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	Unclear	Unclear	Unclear	Unclear
	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	No	No	No	No
	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	No	No	No	No
	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	Unclear	Unclear	Unclear	Unclear
D2c	Are the utilities incorporated into the model appropriate?	Partly	Unclear	Yes	Unclear
	Is the source for the utility weights referenced?	No	No	Partly	No
	Are the methods of derivation for the utility weights justified?	No	No	No	No
D3	Have all data incorporated into the model been described and referenced in sufficient detail?	No	No	No	No
	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	Unclear	Unclear	Unclear	Unclear
	Is the process of data incorporation transparent?	Unclear	Unclear	Unclear	Unclear
	If data have been incorporated as distributions, has the choice of distribution for each parameters been described and justified?	No	No	No	No
	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	Unclear	Unclear	Unclear	Unclear
D4	Have the four principal types of uncertainty been addressed?	Unclear	Unclear	Unclear	Unclear
	If not, has the omission of particular forms of uncertainty been justified?	No	No	No	No
D4a	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	No	Unclear	Partly	No

D4b	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	Partly	Unclear	Unclear	No
D4c	Has heterogeneity been dealt with by running the model separately for different sub-groups?	No	No	No	No
D4d	Are the methods of assessment of parameter uncertainty appropriate?	Unclear	Unclear	Partly	Unclear
	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	No	No	No	No
CONSISTENCY (C)					
C1	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	No	No	No	No
C2	Are the conclusions valid given the data presented?	Yes	Yes	Yes	Yes
	Are any counterintuitive results from the model explained and justified?	No	No	No	No
	If the model has been calibrated against independent data, have any differences been explained and justified?	No	No	No	No
	Have the results of the model been compared with those of previous models and any differences in results explained?	No	No	No	No

Table 34: Philips checklist for Full papers

Quality Criteria	Question(s) for critical appraisal	Response by study Jalali et al (10)	Shih et al (12)	Velikanova et al (13)	Weidlich et al (14)
STRUCTURE (S)					
S1	Is there a clear statement of the decision problem?	Yes	Yes	Yes	Yes
	Is the objective of the evaluation and model specified and consistent with the stated decision problem?	Yes	Yes	Yes	Yes
	Is the primary decision maker specified?	No	No	Partly	No
S2	Is the perspective of the model stated clearly?	Yes	Partly	Yes	Yes
	Are the model inputs consistent with the stated perspective?	Yes	Yes	Yes	Yes
	Has the scope of the model been stated and justified?	Yes	Yes	Yes	Yes
	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Partly	Yes	Yes	Yes
S3	Has the evidence regarding the model structure been described? Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Partly	Yes	Yes	Yes
	Are the sources of data used to develop the structure of the model specified?	Yes	Yes	Yes	Partly
	Are the causal relationships described by the model structure justified appropriately?	Yes	Partly	Partly	Partly
S4	Are the structural assumptions transparent and justified?	Partly	Yes	Yes	Yes
	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Partly	Yes	Yes	Yes
S5	Is there a clear definition of the options under evaluation?	Yes	Yes	Yes	Yes
	Have all feasible and practical options been evaluated?	No	Yes	No	No
	Is there justification for the exclusion of feasible options?	Partly	Yes	Partly	No

S6	Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	Yes	Yes	Yes	Yes
S7	Is the time horizon of the model sufficient to reflect all important differences between options?	Yes	Yes	Yes	Yes
	Is the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?	Yes	Partly	Partly	Partly
S8	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?	Unclear	Yes	Yes	Yes
S9	Is the cycle length defined and justified in terms of the natural history of disease?	Yes	Yes	Partly	Partly
DATA (D)					
D1	Are the data identification methods transparent and appropriate given the objectives of the model?	Yes	Yes	Partly	Partly
	Where choices have been made between data sources, are these justified appropriately?	Partly	Yes	Partly	Partly
	Has particular attention been paid to identifying data for the important parameters in the model?	Yes	Yes	Partly	Partly
	Has the process of selecting key parameters been justified and systematic methods used to identify the most appropriate data?	Partly	Partly	Partly	Partly
	Has the quality of the data been assessed appropriately?	Partly	Partly	Partly	Partly
	Where expert opinion has been used, are the methods described and justified?	N/A	No	No	No
D2	Is the pre-model data analysis methodology based on justifiable statistical and epidemiological techniques?	Unclear	Yes	Unclear	Unclear
D2a	Is the choice of baseline data described and justified?	Yes	Yes	Yes	Yes
	Are transition probabilities calculated appropriately?	Yes	Yes	Unclear	Unclear
	Has a half cycle correction been applied to both cost and outcome?	Unclear	Unclear	Unclear	Not stated

	If not, has this omission been justified?	No	No	No	No
D2b	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	Yes	Yes	Unclear	Unclear
	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	Yes	No	Yes	Partly
	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	Yes	Partly	Partly	Partly
	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	No	Partly	No	No
D2c	Are the utilities incorporated into the model appropriate?	No	Yes	Partly	Partly
	Is the source for the utility weights referenced?	Yes	Yes	Yes	Yes
	Are the methods of derivation for the utility weights justified?	Partly	Partly	Partly	Partly
D3	Have all data incorporated into the model been described and referenced in sufficient detail?	No	Yes	Partly	No
	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	Yes	Yes	Yes	Yes
	Is the process of data incorporation transparent?	Yes	Yes	No	No
	If data have been incorporated as distributions, has the choice of distribution for each parameters been described and justified?	Partly	Partly	Partly	No
	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	No	Partly	Unclear	No
D4	Have the four principal types of uncertainty been addressed?	Partly	Partly	Partly	Partly
	If not, has the omission of particular forms of uncertainty been justified?	No	No	No	No
D4a	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	No	No	Partly	Partly

D4b	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	No	No	No	No
D4c	Has heterogeneity been dealt with by running the model separately for different sub-groups?	No	No	No	No
D4d	Are the methods of assessment of parameter uncertainty appropriate?	Partly	Yes	Partly	Partly
	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Partly	Yes	Partly	No
CONSISTENCY (C)					
C1	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	No	No	No	No
C2	Are the conclusions valid given the data presented?	Yes	Yes	Yes	Yes
	Are any counterintuitive results from the model explained and justified?	N/A	N/A	N/A	N/A
	If the model has been calibrated against independent data, have any differences been explained and justified?	N/A	N/A	N/A	N/A
	Have the results of the model been compared with those of previous models and any differences in results explained?	Yes	Yes	Yes	Yes

Appendix 5 – UK N S C reporting checklist for evidence summaries

All items on the UK N S C Reporting Checklist for Evidence Summaries have been addressed in this report. A summary of the checklist, along with the page or pages where each item can be found in this report, is presented in Table 35.

Table 35: UK NSC reporting checklist for evidence summary

Section	Item	Page no.
Title and summaries		
Title Sheet	Identify the review as a UK N S C Evidence summary	Title page
Plain English summary	Plain English description of the executive summary.	5
Executive summary	Structured overview of the whole report. To include: the purpose/aim of the review; background; previous recommendations; findings and gaps in the evidence; recommendations on the screening that can or cannot be made on the basis of the review	7
Introduction and Approach		

Section	Item	Page no.
Background and objectives	Background – Current policy context and rationale for the current review – for example, reference to details of previous reviews, basis for current recommendation, recommendations made, gaps identified, drivers for new reviews	11
	Objectives – What are the questions the current evidence summary intends to answer? – statement of the key questions for the current evidence summary, criteria they address, and number of studies included per question, description of the overall results of the literature search.	13
	Method – briefly outline the rapid review methods used.	14
Eligibility for inclusion in the review	State all criteria for inclusion and exclusion of studies to the review clearly(PICO, dates, language, study type, publication type, publication status etc.) To be decided a priori	14
Appraisal for quality/ risk of bias tool	Details of tool/ checklist used to assess quality, e.g. QUADAS 2, CASP, SIGN, AMSTAR.	17
Search strategy and study selection		
Databases/ sources searched	Give details of all databases searched (including platform/ interface and coverage dates) and date of final search.	17 & 32 (Appendix 1)

Section	Item	Page no.
Search strategy and results	Present the full search strategy for at least one database(usually a version of Medline), including limits and search filters if used. Provide details of the total number of (results from each database searched), number of duplicates removed, and the final number of unique records to consider for inclusion.	32 (Appendix 1)
Study selection	State the process for selecting studies – inclusion and exclusion criteria, number of studies screened by title/abstract and full text, number of reviewers, any cross checking carried out.	17 & 36 (Appendix 2)
Study level reporting of results (for each key question)		
Study level reporting, results and risk of bias assessment	For each study, produce a table that includes the full citation and a summary of the data relevant to the question (for example, study size, PICO, follow-up period, outcomes reported, statistical analyses etc.). Provide a simple summary of key measures, effect estimates and confidence intervals for each study where available. For each study, present the results of any assessment of quality/risk of bias.	Study level reporting: 40-78 Quality assessment: 79-86
Question level synthesis		
Description of the evidence	For each question, give numbers of studies screened, assessed for eligibility, and inclusion in the review, with summary reasons for exclusion	18

Section	Item	Page no.
Combining and presenting the findings	Provide a balanced discussion of the body of evidence which avoids over reliance on one study or set of studies. Consideration of four compartments should inform the reviewer's judgement on whether the criterion is "met", "not met" or "uncertain": quantity; quality; applicability and consistency.	19
Summary of findings	Provide a description of the evidence reviewed and included for each question, with reference to their eligibility for inclusion. Summarise the main findings including the quality/ risk of bias issues for each question. Have the criteria addressed been "met", "not met" or "uncertain"?	30
Review Summary		
Conclusions and implications for policy	Do findings indicate whether screening should be recommended? IS further work warranted? Are there gaps in the evidence highlighted by the review?	31
Limitations	Discuss limitations of the available evidence and of the review methodology if relevant.	31

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