UK National Screening Committee

Cost-effectiveness modelling of Newborn Screening for Spinal Muscular Atrophy

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

Contents

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List of abbreviations

BSC	Best supportive care
BRND	Broad range of normal development
DBS	Dried blood spot
ddPCR	Digital droplet polymerase chain reaction
DHSC	Department of Health and Social Care
GP	General Practitioner
HST	Highly specialised technology
ICER	Incremental cost-effectiveness ratio
ISE	In-service evaluation
IV	Intravenous
LY	Life years
MRI	Magnetic Resonance Imaging
NBS	Newborn blood spot
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PCR	Polymerase chain reaction
PedSQL	Pediatric Quality of Life Inventory
PICO	Population, Interventions, Comparators and Outcomes
PV	Permanent ventilation
QALY	Quality-Adjusted Life Year
ScHARR	Sheffield Centre for Health and Related Research
SCID	Severe Combined Immunodeficiency
SMA	Spinal Muscular Atrophy
SMN	Survival motor neuron
UK	United Kingdom
UK NSC	United Kingdom National Screening Committee
WHO	World Health Organisation

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Plain English summary

Spinal muscular atrophy (SMA) is a genetic disease, with potential for lethal consequences. If babies develop symptoms, especially for certain types of SMA, the treatment may not work as well. It is suggested that newborn blood spot (NBS) screening, where all newborn babies are tested for SMA, can help to identify babies before they show signs or symptoms. This allows treatment to start before symptoms (i.e. presymptomatic treatment) which is found to be more effective than treatment after symptoms develop. However, it is not clear whether the additional costs of NBS screening outweigh the benefits provided by earlier treatment.

A computer model was developed to understand the value for money (i.e. cost-effectiveness) of NBS screening compared to the current care pathway. This report details the methods of this computer modelling approach and input data used, as well as the cost-effectiveness results.

The model includes different parts: a screening part which predicts the number of patients currently identified using NBS screening and the number of patients with missed diagnosis; a 3-year short-term part which uses data on how well the treatments can help patients achieve walking and/or normal function based on published clinical studies, and a long-term part which predicts the lifetime costs and benefits for the patients.

There are 3 treatments available for patients with SMA. Onasemnogene abeparvovec (Zolgensma) is available routinely in the NHS, but only for severe patients, while the other 2 treatments nusinersen (Spinraza) and risdiplam (Evrysidi) are currently under special funding arrangements in England. It is not clear whether they will be funded routinely through the NHS in the future as the National Institute for Health and Care Excellence (NICE) is currently evaluating these 2 treatments, and a decision will not be made until at least November 2025. Also, all the treatments are provided at a discount to the NHS and these costs/discounts are not publically available. Only the list prices (i.e. the initial price set by the drug manufacturers before any discounts or rebates) are available, and without the ‘real’ cost to the NHS, it is difficult to estimate the value for money of these treatments.

To address these uncertainties, different analyses were done in the computer model. Compared with current practice and assuming all 3 drugs are available, implementing NBS screening would prevent each year 2 babies requiring permanent ventilation, around 3 early deaths, and about 30 babies being confined to a sitting state. Implementing NBS screening also enables about 37 more babies to live a broadly normal life. However, NBS screening will identify around 3 babies who will not be affected until adulthood, if at all, and this may be detrimental to their health and wellbeing.

All the analyses suggested that implementing NBS screening could result in better outcomes and lower costs compared current approach, and the cost savings would depend on the treatments used and the price of treatments to the NHS.

Scientific summary

Background

Spinal muscular atrophy (SMA) is an autosomal recessive disease involving degeneration of the alpha motor neurons in the spinal cord resulting in symmetrical muscle weakness and atrophy, with the impact upon the muscles used to support breathing leading to lethal consequences. Newborn blood spot (NBS) screening allows babies to be diagnosed before they show signs or symptoms, and it is widely acknowledged that presymptomatic treatment is more effective than symptomatic treatment. This report details methods of the modelling approach developed by Sheffield Centre for Health and Related Research (ScHARR), input data for the cost-effectiveness model of NBS screening for SMA, as well as the cost-effectiveness results.

Methods

The methods and inputs were developed through online workshops conducted with key experts and findings from several systematic reviews (i.e. reviews of cost-effectiveness models of NBS screening for SMA, as well as reviews on presymptomatic treatment for SMA and accuracy of newborn screening for SMA).

A de novo model was developed to estimate the cost-effectiveness of NBS screening for SMA, informed by key clinical trials and relevant published literature. The model uses a decision tree (for the screening phase) followed by a 3-year short-term model (for incorporating treatment effectiveness based on clinical study data) and long-term modelling (for extrapolation based on survival modelling). The aim of the model is to estimate the incremental cost per Quality-Adjusted Life Year (QALY) gained through NBS screening for SMA compared to current practice for the UK i.e. no NBS screening followed by treatment. A (hypothetical) no-screening plus no treatment/best supportive care (BSC)[i] scenario was also included as comparator.

Analyses

Given the uncertainty in the reimbursement status of the treatments in the future and the lack of "actual" prices, 4 different analyses were performed:

- using all the treatments currently eligible and using list prices
- using all the treatments currently eligible and using price discounts
- using Zolgensma only and using list prices
- using Zolgensma only and using price discounts

[i] BSC refers to symptom management/watch and wait for cases of milder disease or it refers to palliative type care for patients with SMA type 0 and those with very severe disease

In the base case analyses, costs and outcomes were discounted at 3.5% per year and the analyses were from health and social care sector perspective, and mean values of parameters were used to estimate cost-effectiveness (i.e. cost per QALY) results.

Results

Using an annual cohort of 600,000 newborns in the UK and an incidence rate of 1 in 8200 for SMA results in 73.17 cases of SMA. In the No NBS screening arm of the model, 0.73 cases of SMA were detected presymptomatically via family history with the rest of 72.44 cases detected symptomatically. In the NBS screening arm of the model, most of the cases (n=69.44) of SMA were detected presymptomatically with the rest of 3.73 cases detected symptomatically (i.e. the 5% of patients who do not have homozygous deletions in SMN1).

Compared with current practice of No NBS screening and assuming all 3 drugs are available, NBS screening would prevent each year 2 cases requiring permanent ventilation, around 3 early deaths, and about 30 cases being confined to a sitting state. NBS screening also enables about 37 more cases to live a broadly normal life. However, NBS screening will identify around 3 cases with 5 SMN2 copies, those who will not be affected until adulthood, if at all, and this may be detrimental to their health and wellbeing.

An additional cost of £6.7 million is required to operationalise NBS screening each year which is offset by the long-term cost savings due to lower health care costs. All the analyses suggested that NBS screening dominates No NBS screening i.e. NBS screening has higher QALYs and lower costs compared to No NBS screening. The cost savings depended on the treatment mix used and the price of treatments (i.e. whether list price was used or whether discounts were applied).

However, NBS screening is not cost-effective when compared to BSC in the analysis using all available treatments and list prices. In the other three analyses (i.e. using all available treatments assuming discounts, using zolgensma only and at list price, and using zolgensma only with price discounts), NBS screening is cost-effective when compared to BSC at thresholds of £100,000/QALY used for the National Institute for Health and Care Excellence (NICE) highly specialised technologies (HSTs). However, when typical NICE thresholds of £20,000/QALY to £30,000/QALY are used, NBS screening is not cost-effective when compared to BSC.

Key uncertainties and limitations

NICE is currently appraising nusinersen and risdiplam for symptomatic and presymptomatic treatment of SMA, with the recommendations scheduled for November 2025. As such, there is substantial uncertainty in the reimbursement status of these treatments in the future. It should also be noted that the costs of treatments are under confidential patient access schemes in the NHS, and as such, the “actual” prices of these treatments are unknown.

There is also uncertainty in the effectiveness of presymptomatic and symptomatic treatment, with limited longer-term data. In particular, there is uncertainty in terms of the impact of

diagnostic delay on the number of patients becoming symptomatic with Type 1 SMA, and subsequently the impact on outcomes achieved. Also, there is uncertainty in the costs in the sitting health state and if the costs are lower than those used in the model, NBS screening could be less cost-effective.

Conclusions

The analyses from the *de novo* model suggest that NBS screening is cost-effective compared to current practice of No NBS screening and symptomatic treatment, but may not be cost-effective when compared to the hypothetical BSC arm. The cost-effectiveness of NBS screening is dependent on the reimbursement status (uncertain till at least November 2025) and the actual prices of the treatments (which are under confidential discounts).

Introduction

Background

Spinal muscular atrophy (SMA) is an autosomal recessive disease involving degeneration of the alpha motor neurons in the spinal cord resulting in symmetrical muscle weakness and atrophy, with the impact upon the muscles used to support breathing leading to lethal consequences. SMA is traditionally categorised into 5 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).

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 2 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.

Newborn blood spot (NBS) screening allows babies to be diagnosed before they show signs or symptoms, and it is widely acknowledged that presymptomatic treatment is more effective than symptomatic treatment. The cost-effectiveness of NBS screening for SMA is dependent on the opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) and the costs and benefits of earlier treatment compared to delayed treatment.

There are now 3 treatments available for patients with SMA. Of these, nusinersen (Spinraza) and risdiplam (Evrysidi) are recurrent treatments and the third treatment, onasemnogene abeparvovec (Zolgensma), is a one-off gene therapy. Symptomatic treatment is based on SMA type and presymptomatic treatment is based on identification of SMN2 copy numbers. This is because in general, patients with more SMN2 copies have less severe SMA symptoms. However, as previously noted, there is uncertainty around the mapping of genotypes to phenotypes (i.e. explicit modelling of the link between SMN2 copy number and SMA type).

Reimbursement status of the treatments for SMA

The reimbursement status of symptomatic and presymptomatic treatments for SMA currently in England in the NHS, and any restrictions on populations eligible for treatment are sourced from the National Institute for Health and Care Excellence (NICE) website, as reported in Table 1 below. It should be noted all 3 treatments are approved for use in Scotland without any managed access agreements.

However, NICE is currently appraising nusinersen and risdiplam for symptomatic and presymptomatic treatment of SMA, with the recommendations scheduled for November 2025. As such, there is substantial uncertainty in the reimbursement status of the treatments in the future.

To address this issue, the base case analyses assumed all treatments would be available according to their current eligibility as reported in Table 1 below, and a scenario analysis was performed assuming only Zolgensma is available (i.e. if nusinersen and risdiplam were not approved).

Table 1. Reimbursement status of treatments for SMA

	Reimbursement status	**Population**	**Details**
Current status of Presymptomatic treatment in the NHS in England			
Nusinersen (Spinraza)	Yes, but not for routine NHS use	For pre-symptomatic SMA patients	Under Managed Access Agreement + Commercial offer
Onasemnogene abeparvovec (Zolgensma)	Yes, for routine use	5q SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene in babies aged 12 months and under	Patient access scheme
Risdiplam	Yes, but not for routine NHS use	pre-symptomatic SMA and 1 to 4 SMN2 copies	Under Managed Access Agreement + Patient access scheme
Current status of symptomatic treatment in the NHS in England			

Nusinersen (Spinraza)	Yes, but not for routine NHS use	SMA types 1, 2 or 3	Under Managed Access Agreement + Commercial offer
Onasemnogene abeparvovec (Zolgensma)	Yes, for routine use	SMA Type 1 (5q SMA with a biallelic mutation in the SMN1 gene and clinical diagnosis of Type 1 SMA in babies they are 6 months or younger, or they are aged 7 to 12 months, and their treatment is agreed by the national multidisciplinary team)	Patient access scheme/Commercial arrangement
Risdiplam	Yes, but not for routine NHS use	Clinical diagnosis of SMA types 1, 2 or 3	Under Managed Access Agreement + Patient access scheme

Price of treatments for SMA

It should also be noted that the costs of treatments are under confidential patient access schemes in the NHS, and as such, the “actual” prices of these treatments are unknown. Without access to this confidential pricing data, the list prices for the treatment costs were used in the base case analyses. However, analyses were performed using discounts to understand the impact on cost-effectiveness.

Methods

Overview

This report details methods of the modelling approach developed by ScHARR, as well as input data for the cost-effectiveness model of NBS screening for SMA. The methods and inputs were developed through online workshops conducted with key experts and findings from several systematic reviews (i.e. reviews of cost-effectiveness models of NBS for SMA, as well as reviews on presymptomatic treatment for SMA and accuracy of newborn screening for SMA).

A systematic review of cost-effectiveness models of NBS for SMA, supplemented by citation searching and focused database searching, identified 9 studies of cost-effectiveness models addressing NBS screening for SMA (1–9) This literature was used to identify options for structuring the model. To identify sources for model parameterisation, the outputs from the review of cost-effectiveness models was supplemented by citation searching and focused database searching, with priority given to UK-based studies where available. Systematic review of studies of presymptomatic treatment for SMA was used to estimate the treatment effectiveness and accuracy of newborn screening for SMA was identified from a review of studies of newborn screening for SMA.

Four online workshops were conducted in September 2023, October 2023, May 2024 and November 2024 with around 20 participants in each workshop. The aim of the first workshop was to finalise the model specification and assumptions, the second workshop aimed to identify best sources of data for populating the model and the third workshop addressed key uncertainties in the modelling and input data. The fourth workshop involved presenting the draft results and identifying the changes needed to be made in the base case analyses. The workshop participants included experts in NBS screening, SMA, clinicians, health economic modelling and stakeholders from the UK National Screening Committee (NSC) in the Department of Health and Social Care (DHSC) and SMA Alliance. Slide decks were developed to provide an overview of the findings from the literature identified in the systematic reviews, and the slide decks also included specific questions to be discussed at the workshops.

The next sections outline the methods including detailed model specification, the best sources of data for populating the model (identified from both the published literature and online workshops) and the analyses to be performed. The model specification section describes the PICO (Population, Interventions, Comparators and Outcomes), modelling approach, model structure, scope and key assumptions. The section on input parameters describes the best sources of data for epidemiology and natural history of SMA, diagnostic accuracy of NBS, effectiveness of presymptomatic and symptomatic treatment of SMA, long-term disease progression of SMA (including mortality risks), costs and utilities. The analyses section describes the base case (i.e. the appropriate model settings e.g. discount rate, perspective and assumptions) and key sensitivity analyses used to estimate the incremental cost per QALY gained through use of NBS screening for SMA compared to current practice for the UK.

Model specification

A *de novo* model was developed to estimate the cost-effectiveness of NBS for SMA, informed by key clinical trials and relevant published literature. In the base case analyses, costs and outcomes were discounted at 3.5% per year and the analyses were from health and social care sector perspective. However, sensitivity analyses were performed using discount rates of 1.5% for costs and health effects.

The aim of the model is to estimate the incremental cost per QALY gained through NBS screening for SMA compared to current practice for the UK. As such, the PICO for the model is defined as below in Table 2. As well as pharmacological treatments, patients also receive best supportive care (BSC). BSC refers to symptom management/watch and wait for cases of milder disease (SMA type 4 or 5+ SMN2 copies) where patients enter a watch and wait pathway based on symptom management. For patients who are very ill, BSC refers to palliative type care (e.g. for patients with SMA type 0 with very severe disease at the time of diagnosis).

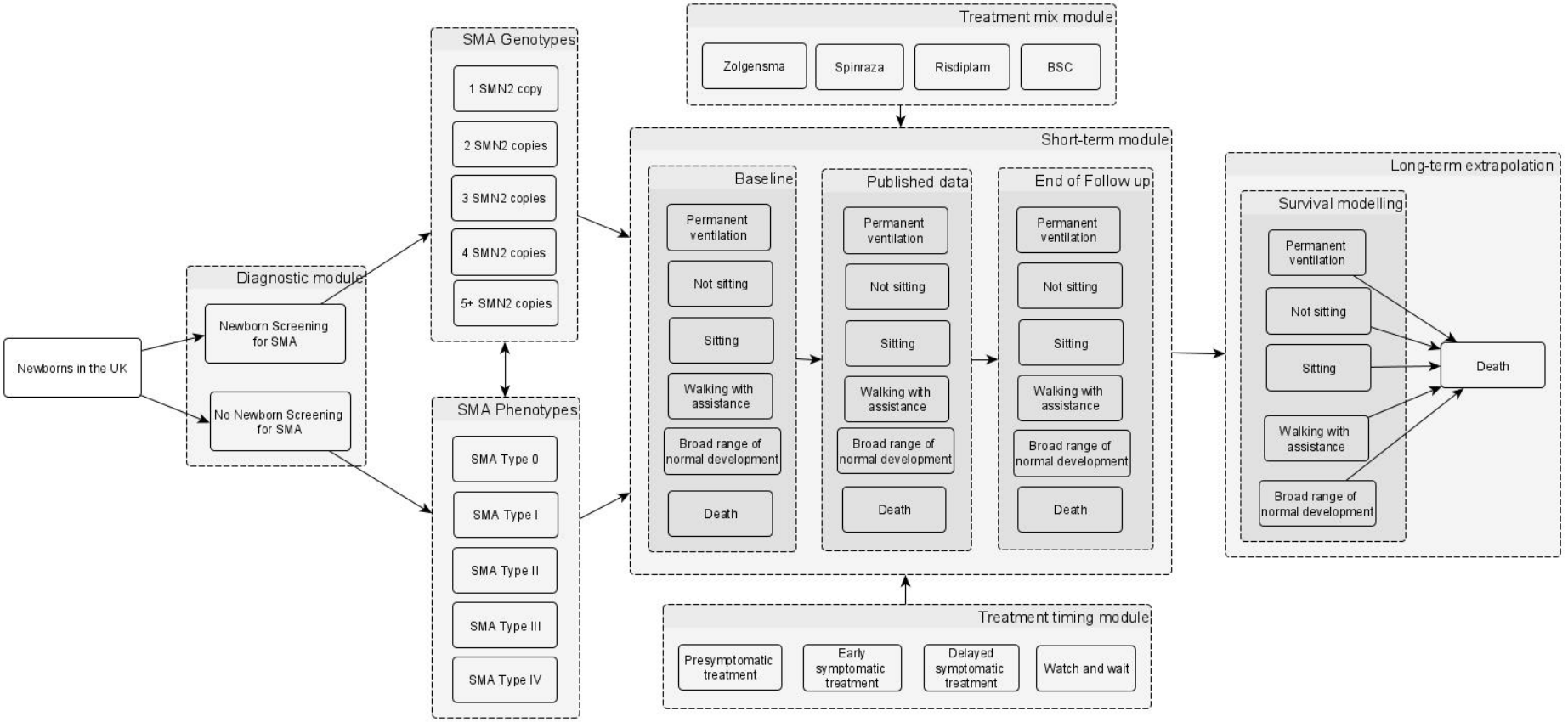
Table 2. PICO (Population, Interventions, Comparators and Outcomes)

Item	**Description**
Population	Newborns in England and Wales
Interventions	Newborn bloodspot screening and pharmacological treatment of presymptomatic or early symptomatic SMA. The pharmacological treatment options include: • Nusinersen (Spinraza) • Onasemnogene abeparvovec (Zolgensma)* • Risdiplam (Evrysdi) Note that some patients might be symptomatic before receiving treatment. Rather than receiving pharmacological treatment for SMA, some patients may receive BSC or go on a watch and wait pathway.
Comparators	No screening and pharmacological treatment of delayed symptomatic SMA. The pharmacological treatment options include: • Nusinersen (Spinraza) • Onasemnogene abeparvovec (Zolgensma)* • Risdiplam (Evrysdi)

	Note that some patients might receive presymptomatic treatment. Also, in line with typical health economic practice, a (hypothetical) no-screening plus no treatment/BSC scenario was included as comparator.
Outcomes	Cost-effectiveness of newborn screening for SMA from an NHS health and social care perspective • Incremental costs • Incremental quality adjusted life years (QALYs) • Incremental cost-effectiveness ratio (ICERs) Resource use estimates for implementing screening for SMA • Number of tests • Lab technician time • Equipment costs • Ongoing quality assurance costs Costs for setting up of NBS for SMA • costs of setting up pathways • screening administration costs • initial quality assurance costs

*will be referred as Zolgensma henceforth in this report

Figure 1. Simplified model structure of NBS screening for SMA



Footnote: Although not depicted in the figure above, a (hypothetical) no-screening plus no treatment/BSC scenario will also be included as comparator. In the short-term module box, the "baseline", "published data" and "end of follow up" in the different columns relate to the 6-monthly time intervals, where data on the proportions of patients in the different health states are sourced from the key clinical studies of the different treatments.

Model Overview

The model structure, shown in Figure 1, reflects the approach using decision tree (for the screening phase) followed by a 3-year short-term model (for incorporating treatment effectiveness based on clinical study data) and long-term modelling (for extrapolation based on survival modelling). This modelling approach was considered appropriate by the key experts in the online workshops, and this was also the most common approach in the studies identified in the systematic review of cost-effectiveness models of NBS screening for SMA.

The model population is a hypothetical cohort of newborns in the UK, some with SMA. Model cycle length is six-monthly, based on the availability of treatment effectiveness data. There are different modules in the model i.e. screening, treatment mix, treatment effectiveness, short-term and long-term modelling. A brief description of each is provided here, with a detailed explanation of the data used presented in subsequent sub-sections.

The screening phase models the population (newborns in the UK) and includes the incidence of SMA, the proportions of different genotypes, ensuring the mapping between genotypes and phenotypes so that the population in the no NBS screening arm is the same as in the NBS screening arm. The short-term model is a 3-year short-term model (for incorporating treatment effectiveness based on clinical study data) and the long-term extrapolation model is based on survival modelling.

NBS and No NBS

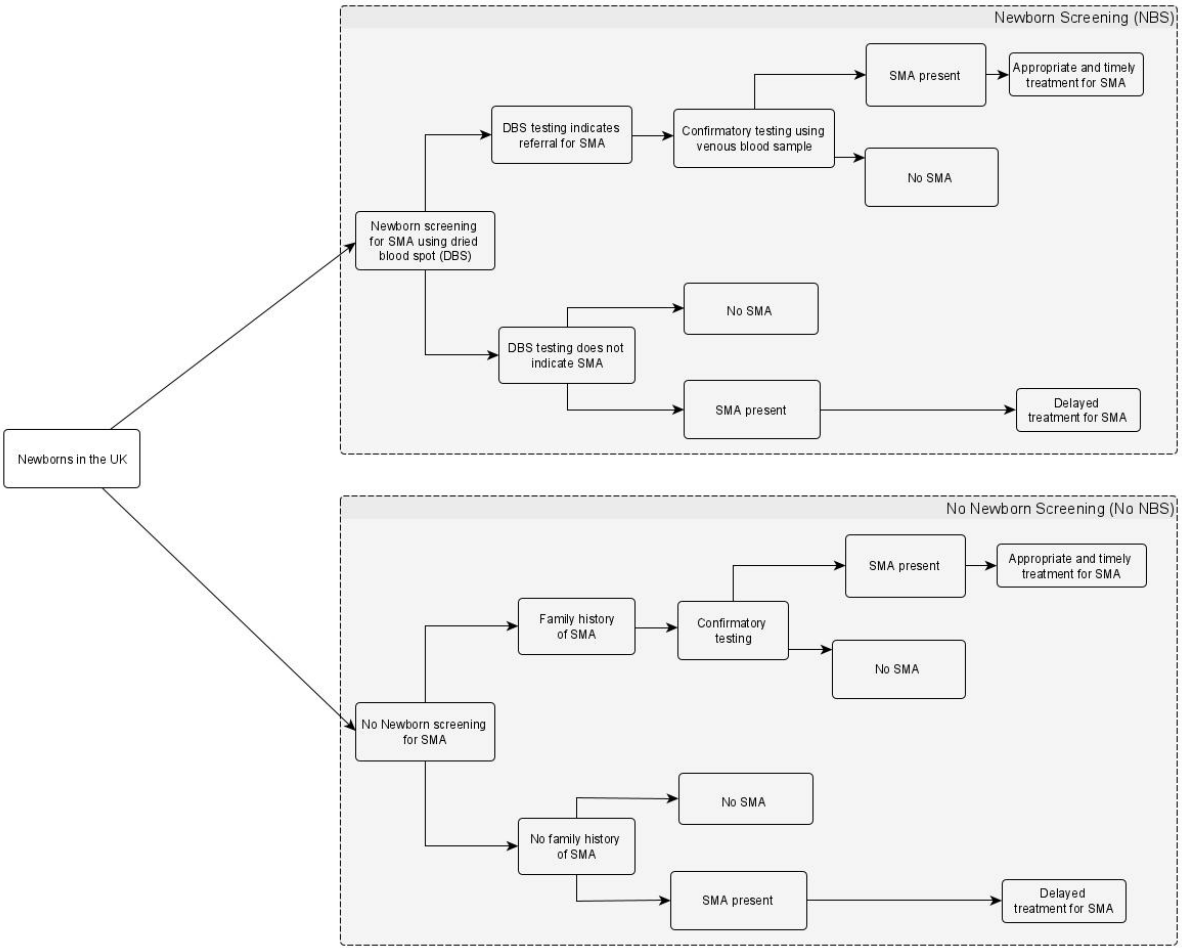
The NBS and No NBS screening parts of the model are presented in Figure 2 and described in more detail below.

For NBS screening pathway, the clinical experts suggested to characterise the pathway into 2 phases: the first phase involves the testing performed on the dried bloodspot (DBS) prior to referral for SMA and the second phase involves the confirmatory testing using venous blood sample at the meeting with a SMA clinician.

The DBS testing will include PCR test, likely a real time reverse transcription PCR (real time RT-PCR test), and if the PCR test suggests SMA, then a) the clinician would be alerted to schedule an appointment with the patients' family, and b) digital droplet PCR (ddPCR) would be performed on the same DBS sample to confirm SMN1 deletion or mutation, and to establish the SMN2 copy number.

If SMA is suspected, the SMN2 copy number information would be sent to the clinician prior to the meeting with family of the newborn with suspected SMA. In the meeting, venous blood sample would be extracted to perform the confirmatory genetic testing on this new venous blood sample. Note that the initial PCR test will not detect other variants (in the 5% of patients who do not have homozygous deletions in SMN1).

Figure 2. Simplified description of the NBS screening arm and the No NBS screening arm



Based on the accuracy of the tests in the NBS screening arm, the model estimates the proportions of patients with different SMN2 copies (1,2,3,4,5+) in the 4 groups (true/false positives/negatives). Patients correctly identified receive appropriate care with true negatives correctly identified as not having SMA, and the true positives correctly identified as having SMA and receiving early and presymptomatic treatment. This also includes a proportion of early screen detected patients with SMA Type 1 who are symptomatic prior to receiving treatment (due to the early onset of symptoms and/or delays in diagnosis and treatment). The model also includes a very small proportions of patients with SMA missed (i.e. false negatives) during the DBS testing, and these patients are assumed to receive treatment after developing symptoms (i.e. symptomatic treatment due to a false negative result). The model also includes a small proportion of patients without SMA being referred to the clinicians (i.e. false positives) and these will be identified correctly as not having SMA after the genetic testing on venous blood sample, as it is the gold standard for diagnosing SMA.

In the No NBS screening arm, it was assumed that patients with family history of SMA would receive testing for SMA and would be detected presymptomatically, and those without family history of SMA would receive treatment after developing symptoms. Although some patients

with family history of SMA may be symptomatic at birth, given that these are very small numbers, it was assumed in the model that all patients with family history of SMA would be detected presymptomatically.

Short-term model

The short-term (and long-term modelling) is dependent on 3 constructs: the motor function milestones gained, need for permanent ventilation and the time to death.

Data on motor function milestones, permanent ventilation, and mortality over different time points were extracted from the relevant trials/studies (plus additional follow-up data from registry data). It is not possible to estimate transition probabilities without the access to individual level data from the trials/studies. As such, the data for the different interventions during the study period are used directly in the model to capture the proportion of the patients in the different health states at different points in time. These data allow an estimate of the discounted costs and discounted QALYs within the study periods.

The motor function milestones used in the model are sitting, walking with assistance and broad range of normal development, in line with the previous cost-effectiveness analyses in SMA. The clinical trials report data on patients sitting, walking with assistance and walking. As such, those who were walking with assistance at the end of the trial follow-up were assigned to walking with assistance health state in the model, and those who were walking at the end of the trial follow-up were assigned to the broad range of normal development (BRND) health state in the model.

Other motor function milestones such as head control, rolling, crawling, and standing are not modelled as explicit health states in the model. This is due to the interim nature of these milestones, lack of consistent data on these milestones across all the treatments and more importantly, lack of data about the long-term survival of patients with these interim milestones. To account for the exclusion of interim milestones, scenario analyses were undertaken to explore the potential impact of making allowances for different utilities within the broad health states based on motor function milestones used in the model (i.e. sitting, walking with assistance and BRND).

Treatment effectiveness

The treatment effectiveness is based on the proportions of patients receiving the different treatments (Zolgensma, Spinraza, Risdiplam or BSC), either presymptomatically or symptomatically, according to the number of SMN2 copies (1, 2, 3, 4, 5+) in the NBS screening arm and the different SMA types (0, 1, 2, 3, 4) in the no NBS screening arm.

The effectiveness of treatment in both arms of the model (i.e. presymptomatic treatment in NBS screening arm and symptomatic treatment in no NBS screening arm) is captured in terms of the motor function milestones achieved over different time points. The data on motor function milestones achieved over different time points is captured separately for each of the 3 treatments (Zolgensma, Spinraza and Risdiplam) as well as best supportive care for different SMN2 copies (1, 2, 3, 4, 5+) in the NBS screening arm and by SMA types (0, 1, 2, 3, 4) in the no NBS screening arm.

The effectiveness in the NBS screening arm is modelled by combining the motor function milestones separately for different SMN2 copies (1, 2, 3, 4, 5+) based on the treatment proportions, and then combined to understand the effectiveness in the NBS screening arm.

The effectiveness in the no NBS screening arm is modelled by combining the motor function milestones separately for different SMA types (0, 1, 2, 3, 4) based on the treatment proportions.

Long-term model

The long-term model involves the extrapolation of motor function milestones, the need for permanent ventilation, and mortality which is assumed conditional on health states. The long-term model uses 6-monthly time cycles to estimate the lifetime costs and QALYs.

The extrapolation of motor function milestones over lifetime was modelled using different scenarios. The base case scenario assumed that the motor function milestones achieved at the end of the 3 years are sustained until death (i.e. patients stay in the same motor function milestone-based health state until death). A pessimistic scenario for the interventions where a proportion of patients will lose their milestones, were also modelled.

Transition to permanent ventilation state in the model is only possible for patients during the first 36 months and only for those who do not have any motor function milestones i.e. the patients in the 'not sitting' health state. All the other patients who have motor function milestones are not at a risk of transitioning to permanent ventilation.

The model uses different state-specific mortality risks by health state (i.e. a lower mortality risk for patients achieving motor function milestones).

For the proportion of patients alive at the end of the short-term model, the long-term risk of mortality risk associated with each of the health states was modelled by using parametric survival curves from prior published economic models i.e. the mortality in the long-term is modelled using survival curves for each of the motor function milestones. The data on mortality risk associated with each of the health states are described in detail in section on Model Inputs.

The long-term modelling module incorporates a waning treatment effect in order to explore the uncertainty around the long-term effectiveness of treatments, and the model also includes hazard ratios to estimate the impact of assuming better or worse survival.

Key model assumptions

The model includes several assumptions which are described in Table 3 below.

Table 3. Model Assumptions

Assumption/model choice	**Rationale**
This model is populated using published literature, however, has the flexibility to	This model would estimate the 'theoretical' cost-effectiveness of implementing NBS screening for SMA in the UK. The 'real' cost-

Assumption/model choice	Rationale
be re-run using the data from In Service Evaluation (ISE).	effectiveness can be estimated using data from ISE, when available.
The base case analyses assume all treatments are available according their current eligibility as reported in Table 1.	NICE is currently appraising nusinersen and risdiplam for symptomatic and presymptomatic treatment of SMA, with the recommendations scheduled for November 2025. Given this, there is substantial uncertainty in the reimbursement status of the treatments in the future. As such, base case analyses assume all treatments are available while a scenario analysis would be performed assuming only Zolgensma is available (i.e. if nusinersen and risdiplam were not approved).
The model cycle length is 6-monthly i.e. the model calculates patients' status each 6 months.	The 6-month model cycle length was based on the availability of treatment effectiveness data. Given the broad nature of SMA, a cycle length of 6 months is expected to appropriately capture health outcomes and costs, and allow for sufficient flexibility to explore our planned sensitivity and scenario analyses. Note that the costs and benefits of NBS screening will be modelled in detail in the first model cycle.
Same diagnostic accuracy is used across patients with different SMN2 copies.	Clinical experts suggested that this is a reasonable assumption to make given that there is no data on sensitivity/specificity across patients with different SMN2 copies.
Patients with SMA missed during NBS screening (i.e. compound heterozygotes and false negatives) receive treatment after symptom onset.	Approximately 5% of patients with SMA are compound heterozygotes (deletion and point mutation) and a small proportion of patients are missed during NBS screening (due to error), and these patients would be identified symptomatically.
NBS screening will not alter the diagnosis or outcomes of newborns with 1 SMN2 copy.	Clinical experts suggested that newborns with 1 SMN2 copy would be patients with Type 0 SMA, symptomatic at birth and under palliative care as the prognosis for these patients is poor

Assumption/model choice	Rationale
	(death in the first month of life), without expectation of improvement with treatment.
Patients with 5+ SMN2 copies receive annual follow-up and if symptomatic, would receive symptom management as patients with SMA Type 4.	Clinical experts suggested that newborns with 5+ SMN2 copies would be patients with Type 4 SMA, who would be either asymptomatic or have milder symptoms.
The model does not include screening/treatment refusal.	It is acknowledged that screening uptake, though very high, is not 100% and that there may be refusal of treatment for SMA. However, incorporating those factors is beyond the scope of the model. Given the aim is to estimate cost-effectiveness of NBS, 100% adherence was assumed during screening. The effectiveness of treatments was based on trials which already include treatment adherence.
The model does not include combination therapies or bridging treatment.	While some patients with SMA may receive multiple treatments (e.g. risdiplam and nusinersen, or risdiplam or nusinersen after gene therapy) or bridging treatment (e.g. risdiplam or nusinersen while they wait for gene therapy), these are not included in the model as there is no data on outcomes after multiple treatments.
Data from the trials/studies on motor function milestones, permanent ventilation and mortality is used directly in the short-term model.	Robust estimation of disease progression parameters (e.g. transition probabilities) is not possible without the access to individual patient data (IPD) from the trials/studies. As such, the data for the different interventions during the study period will be used directly in the model to estimate short-term costs/QALYs.
Those who were walking with assistance at the end of the trial follow-up were assigned to walking with assistance health state in the model, and those who were walking at the end of the trial follow-up were assigned to	The clinical studies report data on proportions of patients walking with assistance. However, the model is based on milestones of walking with assistance and BRND. In line with the previous models, it was assumed that those who were walking with assistance at the end of the follow-up were assigned to walking with

Assumption/model choice	Rationale
the broad range of normal development (BRND) health state in the model.	assistance health state in the model, and those who were walking at the end of the trial follow-up were assigned to the broad range of normal development (BRND) health state in the model.
Motor function milestones achieved at the end of the follow up are sustained until death.	There is no long-term data on the extrapolation of motor function milestones, and hence the base case analyses assume that these are sustained until death. However, alternative scenario analyses are also considered in the model.
Other motor function milestones such as head control, rolling, crawling, and standing are not modelled as explicit health states in the model.	The motor function milestones used in the model(s) are sitting, walking with assistance and broad range of normal development. However, scenario analyses were undertaken to explore the potential impact of making allowances for different utilities within these broad health states.
Only patients in the 'not sitting' health state can move to permanent ventilation state.	Clinical experts opined that this is a reasonable assumption to make: that patients achieving motor function milestones are not at risk of permanent ventilation.
Patients who are in 'sitting' health state are assumed to have mortality similar to that of SMA type 2 patients.	Patients who can sit are assumed to have similar prognosis as SMA type 2 patients, who are able to sit but not walk.
Patients who are in 'walking with assistance' health state are assumed to have mortality similar to that of SMA type 3 patients.	Patients who can walk with assistance are assumed to have similar prognosis as SMA type 3 patients, who are able to walk.
Utility data used in the base case analysis is derived from several sources.	There is no single source of utility data that is based on robust methodology and has face validity. Scenario analyses were performed using other sources of utility data.

Assumption/model choice	Rationale
Adverse event costs are not included in the model.	Given the nature of SMA, it is difficult to disentangle the adverse events due to treatment from the complications associated with SMA, which are already accounted for in the health state costs. As such, the costs of adverse events are not included in the model.
For model inputs with no evidence-based specified uncertainty range, a range of +/-20% was used.	Inclusion of parameter uncertainty within one-way and probabilistic analysis allows for a reasonable characterization of uncertainty.

SMA: Spinal Muscular Atrophy, QALY: quality-adjusted life year, NICE: National Institute for Health and Care Excellence

Model Inputs for Epidemiology

The epidemiology parameters include the incidence of SMA, proportions of genotypes, and mapping between genotypes and phenotypes.

Incidence

Data on the incidence of SMA was sourced from a recent systematic review(10) which provided data from several countries. The clinical experts suggested that patients from Western Europe were the closest to the UK population, as such, the data from Belgium and Germany were pooled to estimate the incidence of SMA as 1 in 8200 newborns.

Proportions of SMN2 copy numbers

The proportions of different SMN2 copy numbers were sourced from published literature. As before, data on patients from northern Europe (Germany, Belgium and Norway) were used to estimate the proportions of different SMN2 copy numbers as shown below in Table 4. Patients in the NBS screening arm were categorised by the number of SMN2 copies (1, 2, 3, 4, 5+), and the 5+ SMN2 copies category was considered separately to 4 SMN2 copies category as there are no recommended pharmacological treatments for patients with 5+ SMN2 copies.

Data from the US from a large cohort of patients, over 6 million screened babies and 425 confirmed cases of SMA, has recently been published which includes the birth prevalence and the distribution of SMN2 copy numbers (Belter et al 2024). With a birth prevalence of 1 in 14,694 and the distribution of SMN2 copy number shown below this implies a lower incidence and a more severe disease distribution than the Northern European data. This data was included as a sensitivity analysis.

Table 4. Proportions of different SMN2 copy numbers in patients with SMA

Country	N	Proportions of different SMN2 copy numbers

		1	2	3	4	5+
Germany nationwide screening (11)	46	2.00%	43.00%	28.00%	22.00%	4.00%
Germany pilot projects (12)	67	0.00%	46.00%	24.00%	26.00%	4.00%
Belgium (13)	9	0.00%	44.44%	33.33%	22.22%	0.00%
Norway (14)	10	0.00%	50.00%	30.00%	20.00%	0.00%
Overall proportions		0.73%	42.88%	27.76%	25.04%	3.59%
US (15)	425	5%	49%	33%	13%	

Mapping of genotypes to phenotypes

The mapping of genotypes to phenotypes (i.e. explicit modelling of the link between SMN2 copy number and SMA type) was based on data from Calucho et al (16) as shown in Table 5. The Spanish only cohort was used for carrying out the initial mapping as the testing was conducted in the same laboratory and according to the same methodology. However, the Spanish only cohort did not differentiate between types 3 and 4. In order to calculate these proportions, a smaller subset of the international data was used and these proportions were then used to adjust the Spanish only Type 3+ cohort. Given the small numbers of patients with 5+ SMN2 copies and with SMA Type 4, it was assumed that all those with 5+ SMN2 copies would be SMA Type 4.

Table 5. Relationship between SMN2 copy number and SMA Types

SMN2 Copy number	SMA Type 0	SMA Type 1	SMA Type 2	SMA Type 3	SMA Type 4
1	100.00%	0.00%	0.00%	0.00%	0.00%
2	0.00%	88.00%	9.00%	2.77%	0.23%
3	0.00%	6.00%	57.00%	36.72%	0.28%
4	0.00%	0.00%	0.00%	88.40%	11.60%

5+	0.00%	0.00%	0.00%	0.00%	100.00%

Proportions used in the model

Based on data from Tables 4 and 5, the proportions of patients in the NBS screening arm and No NBS screening arm of the model can be estimated as below (Table 6). These proportions are presented in Table 6 along with estimates from the literature on SMA Type distribution. Kekou et al (17) reports on the phenotypes of 361 individuals genetically diagnosed with SMA in Greece over a 24-year period. Konig et al (18) collected data on the incidence of SMA in Germany from neuromuscular centres, genetic institutes and the German patient registries. Data on subtypes of SMA were collected only from neuromuscular centres and the German patient registry for 758 patients. This did not include patients with Type 0 or Type 4. Calucho et al (16) only included the index cases (unrelated) of SMA and the study was designed to assess the correlation between SMA type and SMN2 copy number rather than an epidemiological study of SMA in Spain. All studies are likely to suffer from ascertainment bias with severe patients (Type 0 & 1) less likely to be included due to the high mortality in this cohort and less severe patients (Type 4) also less likely to be included due to potential for under or misdiagnosis in this group.

Table 6. Proportions of patients in different groups in the NBS screening arm and No NBS screening arm of the model

NBS screening arm	**1 SMN2 copy**	**2 SMN2 copies**	**3 SMN2 copies**	**4 SMN2 copies**	**5+ SMN2 copies**
Proportions	0.73%	42.88%	27.76%	25.04%	3.59%
No NBS screening arm	**SMA Type 0**	**SMA Type 1**	**SMA Type 2**	**SMA Type 3**	**SMA Type 4**
Model Proportions	0.73%	39.40%	19.68%	33.52%	6.67%
Ogino et al (19)	N/R	58%	29%	13%	N/R
Calucho et al (16) Spain	N/R	43%	30%	27%	*
Kekou et al (17) Greece	2.5%	40%	26%	30%	1.5%
Kekou et al (17) Germany	N/R	37%	41%	21%	N/R

*All walkers were grouped together as Type 3

Model Inputs for Treatments

Treatment mix

The reimbursement status of symptomatic treatments for SMA currently in the NHS and any restrictions on populations eligible for treatment are sourced from the NICE website as reported in Table 1. However, the elicitation of treatment mix was not constrained by reimbursement status of the treatments, given the status could change in the future. As such, expert opinion was solicited to specify the treatment mix describing the proportions of patients receiving the different treatments (Zolgensma, Spinraza, Risdiplam or BSC), either presymptomatically or symptomatically (based on the calculations in the screening module), according to the different SMN2 copies (1, 2, 3, 4, 5+) in the NBS screening arm and SMA types (0, 1, 2, 3, 4) in the no N BS screening arm.

Table 7 shows the proportions of patients receiving the different treatments in the model, according to the number of SMN2 copies (1, 2, 3, 4, 5+) in the NBS screening arm and SMA types (0, 1, 2, 3, 4) in the no NBS screening arm.

Table 7. Treatment mix in the NBS screening arm and No NBS screening arm

NBS screening arm	**1 SMN2 copy**	**2 SMN2 copies**	**3 SMN2 copies**	**4 SMN2 copies**	**5+ SMN2 copies**
Nusinersen	0%	5%	5%	5%	0%
Zolgensma	0%	85%	85%	0%	0%
Risdiplam	0%	10%	10%	85%	0%
Best Supportive Care (BSC)*	100%	0%	0%	10%	100%
No NBS screening arm	**SMA Type 0**	**SMA Type 1**	**SMA Type 2**	**SMA Type 3**	**SMA Type 4**
Nusinersen	0%	2.5%	10%	10%	0%
Zolgensma	0%	85%	0%	0%	0%
Risdiplam	0%	7.5%	90%	90%	0%
Best Supportive Care (BSC)*	100%	5%	0%	0%	100%

*BSC in NBS screening arm refers to palliative style care for those with 1 SMN2 copy and symptom management for those with 5+ copies, while in No NBS screening arm, BSC refers to palliative style care for those with SMA Type 1 and symptom management for those with SMA Types 3 & 4

Treatment in the NBS screening arm

In the NBS screening arm, the model uses 99.9% sensitivity and specificity for the initial PCR test, and assumes 100% specificity after confirmatory testing (as any false positives would be identified as not having SMA during the genetic testing). Note that the initial PCR test will not detect patients with other variants (i.e. the 5% of patients who do not have homozygous deletions in SMN1), as such the 99.9% sensitivity for the initial PCR test is for the rest of the patients.

Patients correctly identified in the NBS screening arm as having SMA (i.e. the true positives) would receive appropriate care with true positives receiving early and presymptomatic treatment, depending on the SMN2 copy number. Patients with 1 SMN2 copy would have Type 0 SMA and would receive palliative care as the prognosis is poor for these patients (death in the first month of life), without expectation of improvement with treatment. For patients with 2 SMN2 copies, based on published literature, the average time taken for diagnosis and treatment is around 3 weeks. Around half of the patients with 2 SMN2 copies would show symptoms by this time as shown in Table 8, and these patients would receive early symptomatic treatment. Clinical experts suggested that around 1-2% of new patients with 2 SMN2 copies would show symptoms each day, and this would be used to perform scenario analyses with shorter diagnostic time interval of NBS (e.g. 2 weeks compared to the base case of 3 weeks), where more patients with 2 SMN2 copies would receive presymptomatic treatment. All patients with 3 and 4 SMN2 copies would be asymptomatic prior to treatment, as the symptom onset for type 2 and 3 SMA is around 6 months and 2.5 years, respectively. Patients with 5+ SMN2 copies would be under annual follow-up and if symptomatic, would receive symptom management as patients with SMA Type 4.

Patients correctly identified in the NBS screening arm as not having SMA (i.e. true negatives) were assumed to be the same as general population and would not incur any further costs.

Patients with SMA missed during NBS screening (i.e. false negatives and compound heterozygotes) would receive treatment after symptom onset. Approximately 5% of patients with SMA are compound heterozygotes (deletion and point mutation) and a small proportion (0.1%) of patients are missed during NBS screening (due to error), and these patients would be identified symptomatically.

The small proportion of patients who were incorrectly identified as having SMA (i.e. false positives) during the initial PCR test were assumed to be identified as not having SMA during the genetic testing, which has 100% specificity as the gold standard.

Table 8 below describes the treatment timing based on the number of SMN2 copies. Scenario analyses with shorter diagnostic time interval of NBS, where more patients with 2 SMN2 copies would receive presymptomatic treatment were also performed.

Table 8. Treatment timing in the NBS screening arm based on number of SMN2 copies

SMN2 Copies	Presymptomatic treatment	Early Symptomatic treatment	Delayed symptomatic treatment	BSC*
1	-	-	-	100%
2	48%	52%	(False Negatives)	-
3	100%	0%	(False Negatives)	-
4	100%	0%	(False Negatives)	-
5+	-	-	-	100%

*BSC – palliative care for those with 1 SMN2 copies and symptom management for those with 5+ SMN2 copies

Treatment in the No NBS screening arm

In the No NBS screening arm, it was assumed that patients with family history of SMA would receive testing for SMA and would be detected pre-symptomatically. Some patients may be diagnosed at birth or shortly after without NBS screening due to a family history of the disease and would therefore benefit from early diagnosis and treatment. Discussion during the workshops indicated that this is relatively rare occurrence with most families opting for pre-implantation genetic testing or prenatal testing. It was suggested 1% of patients with SMA would be detected via family history and this estimate is used in the base case analysis.

The rest of the 99% of patients with SMA (i.e. those without family history of SMA) would receive treatment after developing symptoms. The average time of symptom onset (i.e. typical age at presentation) is used in the base case analyses as presented in the Table 9 below.

Table 9. Age of symptom onset by SMA Type

SMA Type	Mean age at presentation (i.e. age of symptom onset)
0	At birth
1	3 months
2	12 months
3	2.5 years
4	>18 years

Effectiveness of presymptomatic treatment

The effectiveness of presymptomatic treatment is captured in terms of the motor function milestones achieved over different time points. This data is captured from the pivotal trials separately for each of the 3 treatments (Zolgensma, Spinraza and Risdiplam) based on the number of SMN2 copies, are shown in Tables 10 and 11. It should be noted that the effectiveness data for presymptomatic treatment from pivotal trials was triangulated against other sources (e.g. registry data and other real world data), where available. In the model, the motor function milestones at the end of the study period are carried forward until month 36 (i.e. duration of the short-term period in the model).

As there is no data for the effectiveness of presymptomatic treatment for patients with 4 SMN2 copies, it was assumed to be 100% for all motor function milestones (i.e. same as general population).

Table 10. Effectiveness of Presymptomatic Treatment for patients with 2 SMN2 copies

Zolgensma – based on SPRINT trial reported in supplementary material of Strauss et al 2022b (20) **Number of patients: 14**				
Month	**Not sitting**	**Sitting**	**Walking with assistance**	**Walking w/o assistance**
6	64.3%	35.7%	-	-
12	-	57.2%	35.7%	7.1%
18	-	14.3%	14.3%	71.4%
24	-	14.3%	14.3%	71.4%
Risdiplam – based on RAINBOWFISH trial conference poster reported in Farrar et al 2024 (21) **Number of patients: 5 (3 patients, not included, withdrawn to receive Zolgesma)**				
Month	**Not sitting**	**Sitting**	**Walking with assistance**	**Walking w/o assistance**
6	80%	20%	N/R	-
12	-	80%	N/R	20%
18	-	80%	N/R	20%
24	-	40%	N/R	60%

Nusinersen – based on NURTURE trial reported in Crawford et al 2023 (22) **Number of patients: 15**				
Month	**Not sitting**	**Sitting**	**Walking with assistance**	**Walking w/o assistance**
6	66.7%	33.3%	-	-
12	6.67%	73.3%	20%	-
18	-	40%	40%	20%
24	-	20%	20%	60%
30	-	20%	-	80%
36	-	13.3%	-	86.7%

*Note that those who were walking with assistance at the end of the trial follow-up were assigned to walking with assistance health state in the model, and those who were walking at the end of the trial follow-up were assigned to the broad range of normal development (BRND) health state in the model.

Table 11. Effectiveness of Presymptomatic Treatment for patients with 3 SMN2 copies

Zolgensma – based on SPRINT trial reported in supplementary material of Strauss et al 2022b (20) **Number of patients: 15**				
Month	**Not sitting**	**Sitting**	**Walking with assistance**	**Walking w/o assistance**
6	53.3%	46.7%	-	-
12	6.7%	20%	33.3%	40%
18	-	6.7%	-	93.3%
24	-	6.7%	-	93.3%
Risdiplam – based on RAINBOWFISH trial conference poster reported in Farrar et al 2024 (21) **Number of patients: 13**				
Month	**Not sitting**	**Sitting**	**Walking with assistance**	**Walking w/o assistance**

6	100%	0%	N/R	-
12	-	92%	N/R	8%
18	-	8%	N/R	92%
24	-	0%	N/R	100%
Nusinersen – based on NURTURE trial reported in Crawford et al 2023 (22) **Number of patients: 10**				
Month	**Not sitting**	**Sitting**	**Walking with assistance**	**Walking w/o assistance**
6	40%	60%	-	-
12	-	30%	10%	60%
18	-	-	-	100%
24	-	-	-	100%
30	-	-	-	100%
36	-	-	-	100%

* As there is no data for the effectiveness of presymptomatic treatment for patients with 4 SMN2 copies, it was assumed to be 100% for all motor function milestones (i.e. the same as general population). Also, note that those who were walking with assistance at the end of the trial follow-up were assigned to walking with assistance health state in the model, and those who were walking at the end of the trial follow-up were assigned to the broad range of normal development (BRND) health state in the model.

Effectiveness of symptomatic treatment

The effectiveness of symptomatic treatment, in terms of the motor function milestones achieved over different time points, were captured from the pivotal trials separately for each of the 3 treatments (Zolgensma, Spinraza and Risdiplam) based on the type of SMA, as shown in Tables 12 and 13. The effectiveness data for symptomatic treatment from pivotal trials was triangulated against other sources (e.g. registry data such as SMA Reach and other real world data), where available.

Zolgensma is currently authorised in the UK for patients with SMA Type 1 only, and there is no data on treatment effectiveness of Zolgensma for Type 2 and Type 3 SMA. Given this, the model does not include the possibility of selecting Zolgensma for patients with Type 2 and Type 3 SMA.

Whilst risdiplam is authorised for patients with Type 2 and Type 3 SMA, there is no data on treatment effectiveness in terms of motor function milestones for these patients. As such, for

patients with Type 2 and Type 3 SMA receiving risdiplam, the model will assume that the treatment effectiveness of risdiplam to be the same as that of nusinersen.

Table 12. Effectiveness of symptomatic treatment for patients with Type 1 SMA

Zolgensma – pooled StriveEU & StriveUS (post 18 month based on improvement seen in START extension) Number of patients 55 (StriveEU & Strive US) 10 (START)						
Month	**Dead**	**Permanent Ventilation**	**Not sitting**	**Sitting**	**Walking with assistance**	**Walking w/o assistance**
6	1.8%	-	98.2%	-	-	-
12	3.6%	3.6%	63.6%	27.3%	1.8%	-
18	3.6%	3.6%	38.2%	50.9%	-	3.6%
24	3.6%	3.6%	19.1%	70%	-	3.6%
30	3.6%	3.6%	19.1%	70%	-	3.6%
36	3.6%	3.6%	9.5%	79.5%	-	3.6%
Risdiplam – based on FIREFISH trial reported in Masson et al 2022 (23) **and Deconinick et al 2022** (24) **(conference poster)*** **Number of patients: 41 (Masson et al 2022), 48 (Deconinick et al 2022)**						
Month	**Dead**	**Permanent Ventilation**	**Not sitting**	**Sitting**	**Walking with assistance**	**Walking w/o assistance**
12	7.3%	-	75.6%	17.1%	-	-
24	7.3%	2.4%	46.3%	43.9%	-	-
36	9%	10%	8.1%	66.7%	6.25%	-
Nusinersen – based on data from SHINE Study, Castro et al (25)						
Month	**Dead**	**Permanent Ventilation**	**Not sitting**	**Sitting**	**Walking with assistance**	**Walking w/o assistance**
6	13.9%	15.9%	66.3%	3.9%	-	-

12	17.3%	27.8%	42.4%	12.4%	-	-
18	22.1%	29.5%	25.7%	22.6%	-	-
24	22.1%	29.5%	29.6%	18.7%	-	-
30	22.1%	29.5%	29.6%	18.7%	-	-

* Note that those who were walking with assistance at the end of the trial follow-up were assigned to walking with assistance health state in the model, and those who were walking at the end of the trial follow-up were assigned to the broad range of normal development (BRND) health state in the model.

Table 13. Effectiveness of symptomatic treatment with Nusinersen for patients with Type 2 SMA and Type 3 SMA

Nusinersen for patients with Type 2 SMA – based on ENDEAR reported in Mercuri et al 2018 (26) **with longer follow up estimated from Darras et al 2019** (27)**; Number of patients: 84**				
Month	**Not sitting**	**Sitting**	**Walking with assistance**	**Walking w/o assistance**
6	-	100%	-	-
12	-	76.2%	23.8%	-
18	-	91.7%	8.3%	-
24	-	91.7%	8.3%	-
30	-	90.5%	9.5%	-
36	-	85.7%	9.5%	4.7%
Nusinersen for patients with Type 3 SMA – based on Darras et al 2019 (27) **Number of patients: 17**				
Month	**Not sitting**	**Sitting**	**Walking with assistance**	**Walking w/o assistance**
6	-	100%	-	-
12	-	-	-	100%
18	-	-	-	100%
24	-	-	-	100%

30	-	11.8%	11.8%	78.5%
36	-	11.8%	-	88.2%

* Note that those who were walking with assistance at the end of the trial follow-up were assigned to walking with assistance health state in the model, and those who were walking at the end of the trial follow-up were assigned to the broad range of normal development (BRND) health state in the model.

Incorporating treatment effectiveness data in the model

Each model health state (Permanent Ventilations (PV), Not Sitting, Sitting, Walking with Assistance, Broad Range of Normal Development (BRND)) has a cost and a utility value associated with it to account to the impact of SMA symptoms on the patient. As the model starts from birth, no babies will be sitting or walking at the beginning. However, these babies should not incur the costs and lower utility value associated with the Not Sitting health state as it is part of normal development that they would be not sitting at this age.

In order to account for this, the normal developmental rules as shown in Figure 3 were used to adjust the milestones reported in the pivotal trials (See Tables A1 – A5 in the Appendix). One model cycle (6 months) was allowed over the normal World Health Organisation (WHO) developmental window to account for delays between a child achieving a milestone and their next trial assessment. Some additional assumptions based on the SMA Type or number of SMN2 copy were also used. Detailed description of how these assumptions relate to the treatment effectiveness parameters is outlined in the Appendix.

Figure 3. Normal Development Rules and the order applied

Rule	Starting Health State	Exceptions
1. If they have achieved Walking with Assistance (18 months) or Walking without assistance (24 months) →	BRND	No patients with Type 1 SMA start in the BRND health state as they would need to show delayed milestones to order to present symptomatically
2. If only sitting at 18 months →	Sitting	Does not apply to Type 2 SM A as assume normal development at 6 months

		and begin to lose milestones at 12 months
3. If not sitting at 12 months	Not sitting	If **all** patients eventually sit, no patients start in the Not Sitting health state

Model Inputs for Outcomes

Long-term survival modelling

For the long-term modelling, in line with the feedback from previous NICE appraisals, the model assumes that the patients cannot transition to better motor function milestones beyond the study follow-up period. Based on expert opinion, the scenario analyses include assumptions around whether the patients continue to stay in the same motor function milestones or whether there is treatment waning (i.e. some patients lose their motor function milestones in the long-term).

The mortality risks, based on the health states (i.e. motor function milestones), are sourced from key literature such as the NICE appraisals and published systematic reviews of cost-effectiveness studies of SMA. The mortality in the long-term is modelled using survival curves for each of the motor function milestones, and the model includes hazard ratios to estimate the impact of assuming better or worse survival in scenario analyses.

Table 14. Survival by motor function milestones on treatment

Parameter	**Mean survival**	**Sources**
Permanent ventilation	5 years*	Gregoretti et al (28)
Not Sitting	5 years*	
Sitting	30 years	Zerres and Schoneborn et al (29)
Walking with assistance	70.90 years	Assumption
Broad range of normal development	78.69 years	General population mortality - Assumption

*assumed to be 2 years for patients on BSC

Utilities

Patient utilities were sourced from the published systematic reviews of utilities in SMA and triangulated with expert input and feedback from NICE appraisals. Caregiver disutilities (for false positive cases in the NBS screening arm as well as longer term disutilities caring for patients with SMA) were captured from published systematic reviews of utilities in SMA and expert input.

The utilities for the different health states (based on motor function milestones) used in the base case analyses are derived from different sources, as presented in Table 15. The utilities from Bastida et al are used for the 'permanent ventilation' and 'not sitting' health states, which were assumed to have same utility values. The utility for 'sitting' health state is captured from Tappenden et al. The utilities for 'Walking with assistance' and 'BRND' health states are captured from the mapped values to Pediatric Quality of Life Inventory (PedSQL) data from CHERISH trial, as the patients in the mapping study were all healthy patients. As such, the utilities used in the base case are a combination of different sources.

Table 15. Utilities used in base case analyses

Health State	**Utility**	**Source**
Permanent ventilation	0.19	López-Bastida et al (30)
Not sitting	0.19	
Sitting	0.60	Tappenden et al (31)
Walking with assistance	0.80	Assumption
BRND	0.9	Assumption

Scenario analyses were also performed using utility data from other published literature as shown in Table 16 below.

Table 16. Utilities used in scenario analyses

Health State	**Utilities from Landfelt et al** (32) **(using EQ-5D-5L)**

Permanent ventilation	0.19
Not sitting	0.26
Sitting	0.46
Walking with assistance	0.76
Normal function	General population utility

Model Inputs for Costs

Costs of NBS screening

The resources required for setting up the NBS including laboratory adaptations/equipment, programme and pathway adaptations, cost per baby screened were sourced from previous UK NSC evaluations, such as Severe Combined Immunodeficiency (SCID) screening, where available, and supplemented with expert opinion.

The cost of setting up and running the facilities to test the DBS using ddPCR was estimated via expert opinion and costs from the proposed SMA NBS in-service evaluation (ISE). It has an estimated costs of £75,400 per annum including £24,000 for equipment and maintenance costs, £49,000 for staff costs, and £2,400 for reagent costs (Jim Bonham communication – email 28/11/24). The cost per baby screened will depend on the cohort size, incidence and test characteristics of the PCR test. Assuming 600,000 births per annum (pa) results in a total of 146 tests per annum (i.e. 73 tests per annum on DBS samples + 73 tests pa on liquid blood). Assuming a 10-year amortisation period results in cost of £510 per test (i.e. 75000/120). However, a conservative estimate of £700 per test was used in the model.

Transportation costs for samples has been estimated at £100 per sample based on expert opinion. The time to the clinical service of organising a referral and seeing the patient was estimated via expert opinion and costed using NHS National Costs Collection or the Unit Costs of Health and Social Care.

Table 17. Costs of screening and confirmatory testing

	Cost	**Included costs**	**Source**

qRT-PCR test (DBS)	£7	• Test kit • Staff • Equipment • Laboratory adaptations • Consumables • Quality assurance • IT changes	SCID screening evaluation and expert opinion
ddPCR (DBS and venous blood sample)	£700 per test	• Equipment & maintenance costs • Staff costs • Reagent costs	Expert opinion – proposed SMA screening in-service evaluation (ISE)
Sample transportation	£100	Rapid sample transportation cost	Literature and assumption
Referral to clinician	3x outpatient paediatric neurology Total £1392	Staff costs – referral, outpatient appointment, phlebotomy	Expert opinion and routine data sources

DBS: Dried blood spot, ddPCR: Digital droplet polymerase chain reaction, qRT-PCR: quantitative reverse transcription polymerase chain reaction, SCID: Severe combined immunodeficiency

Costs of symptomatic diagnosis

As shown in Table 18 for patients diagnosed symptomatically, the diagnostic costs were estimated from the literature. A study of Irish patients found they had had on average 5 contacts with health services prior to the diagnosis. This was costed as 5 GP appointments. The number of diagnostic tests is based on an Italian study that estimated the number of diagnostic tests that patients underwent prior to genetic testing. And in line with screening arm, it was assumed that patients would have 2 to 3 neurology appointments for their ddPCR or MRI test and results. A total cost of £2500 for the diagnostic odyssey of patients detected symptomatically was used.

Table 18. Costs of diagnosis in symptomatic patients

Health resource used	Number	Cost	Total	Source
Health visits prior to diagnosis (GP appointment)	5	£49	£245	Carter et al (33)
MRI	1	£309	£309	Maggi et al (34)
Outpatient paediatric neurology	2.5	£464	£1,160	Expert opinion and routine data sources
ddPCR	1	£700	£700	Calculation

Treatment costs

The costs of treatments are under confidential patient access schemes, and without access to this confidential pricing data, the list prices for the treatment costs were used in the base case analyses. These are summarised in Table 19.

However, sensitivity analyses were performed using discounts of 30% for Zolgensma, and 90% for the other 2 drugs to understand the impact on cost-effectiveness. Zolgensma is a one-off treatment, so a lower discount was assumed, while the other 2 drugs have to be administered through the patient's lifetime, so greater discount was assumed.

Table 19. List prices of the treatments

	List price per unit	Dosage	Administration costs	Total annual cost per patient
Nusinersen	£75,000 per vial	Four loading doses (days 0, 14, 28, and 63), and afterwards every 4 months	£700 to £1600 depending on age	£456,500 in year and £227,500 for subsequent years

Zolgensma	£1,795,000	one-time, single-dose of 1.1x1014 vg/kg by IV infusion	£3,500	£1,798,500 (lifetime cost)
Risdiplam	£7,900 per 60-mg (80-ml) vial	if less than 20kg, a vial approximately every 44 days Otherwise, every 12 days	90% of patients would receive via homecare and costs borne by the company	£65,500 if less than 20kg £240,450 otherwise

Nusinersen has a list price of £75,000 per vial and is administered via repeated intrathecal injections. Patients are given four loading doses (days 0, 14, 28, and 63) and thereafter are treated every 4 months for life, resulting in a total annual treatment cost of £450,000 for the first year and £225,000 for subsequent years at the list price. In their submission to NICE, the company assumed 40% of all nusinersen administrations are in an inpatient setting, 30% are in an outpatient setting and the remaining 30% are in a day case setting. The costs for lumbar puncture were taken from NHS Reference Costs using HRG codes HC72A (Diagnostic Spinal Puncture, 19 years and over), HC72B (Diagnostic Spinal Puncture, between 6 and 18 years) and HC72C (Diagnostic Spinal Puncture, 5 years and under). The company calculated weighted mean administration costs of approximately £1,600 for patients aged 5 years and under, £1,450 for those aged between 6 and 18 years and £700 for those aged 19 years and over.

Zolgensma has a list price of £1,795,000 and is administered as one-time, single-dose by intravenous (IV) infusion over approximately 60 minutes at a dose of $1.1x10^{14}$ vector genomes/kilogram. The administration cost is £3,500 based on the NHS Schedule of Reference Costs, using weighted average of codes relating paediatric nervous system disorders and cerebral degenerations or miscellaneous disorders of nervous system (EL- PR01A-E and EL - AA25C-G).

Risdiplam has a list price of £7,900 per 60-mg (80-ml) vial and the dosage for Risdiplam is age and weight dependent: in infants < 2 months, 0.15 mg/kg once a day, in subjects 2 months to 2 years, 0.2 mg/kg, once a day, in those > 2 years and up to 19 kg, 0.25 mg/kg once a day, and in those > 2 years and over 20 kg, 5 mg once a day. In the model, this was implemented as follows: for infants under the age of 2, on average 5.48 vials were used over 6-months, for 2-6 year olds, on average 11.41 vials were used over 6 months, and for those greater than 6 years, the full dose was used which resulted in an average of 15.22 vials over the 6-month period. This assumption was based on risdiplam dosing and data on the average weight by age suggested by WHO. Also, it was assumed that the majority of patients will receive risdiplam via homecare,

the cost for which will be covered by Roche. However, 10% of patients were assumed to choose to have risdiplam administered through the hospital instead of home delivery, and it was assumed that 5 minutes of pharmacist time (cost: £44 per hour) will be required to reconstitute one vial of risdiplam. This resulted in an administrative cost of £66 per 6-month period.

Health state costs

The health state costs were sourced from previous NICE appraisals, and the caregiver and productivity costs were sourced from key published literature including systematic reviews of costs/cost-effectiveness of screening for SMA and review of economic modelling evidence of NICE appraisals.(35)

There is some variation in the health state costs suggested by the companies in their NICE submissions, as noted in Table 20 below. Based on the expert input from the workshops, the model used the costs in the Nusinersen NICE submission but has added additional costs for the Broad Range of Normal Development health state to account for appointments and tests in this population: these have been estimated at £1,000 per cycle for an annual cost of £2,000 per year.

Table 20. Annual costs by health state in the company submissions to NICE

Health State	**Annual Costs in Nusinersen NICE submission**	**Costs in Zolgensma NICE submission**	**Costs in Risdiplam NICE submission**	**Costs used in the model**
Permanent ventilation	£259,371	£283,710	£259,368	£259,330
Not sitting	£148,214	£112,500	£148,212	£148,214
Sitting	£68,322	£67,567	£108,276	£68,312
Walking with assistance	£20,229	£8,333	£21,768	£21,768
BRND	N/A	£8,333	N/A	£2,000

Model Validation and analysis

Model validation

Several approaches were used to validate the model. Firstly, preliminary model structure, methods and assumptions were provided to key stakeholders including patient groups, and clinical experts. Based on feedback from these groups, data inputs used in the model was refined, as needed. Secondly, model input parameters were varied to evaluate face validity of

changes in results. Another modeller, who was not involved in the development of the model, checked the model calculations to ensure no programming bugs are present in the model. Finally, results were compared to other cost-effectiveness models in this therapy area. The outputs from the model were validated against the trial/study data of the interventions and any relevant observational datasets. A face validity check versus the existing England and Wales model findings (4) was also performed.

Outputs of the model

The base case analysis in the model used an NHS and personal social services perspective. In the base case analyses, mean values of parameters were used to estimate cost-effectiveness (i.e. cost per QALY) results. Alongside cost-effectiveness analysis, the model also estimated aggregated and disaggregated resource use for implementing screening for SMA. The model estimated the incremental cost per QALY of screening for SMA compared to current practice for the UK, using the appropriate model settings (e.g. discount rate, perspective) and assumptions.

Base case analyses

Given the uncertainty in the reimbursement status of the treatments in the future and the lack of "actual" prices, the base case analyses included 4 different analyses as described below.

Base case analysis using all available treatments at list price

The base case analysis used treatments currently eligible for the different SMN2 copies (1, 2, 3, 4, 5+) and SMA types (0, 1, 2, 3, 4) according to NICE websites as reported in Table 1. Table 7 presents the treatment mix describing the proportions of patients receiving the different treatments (Zolgensma, Spinraza, Risdiplam or BSC), presymptomatically and symptomatically.

Base case analysis using only zolgensma at list price

Given NICE is currently evaluating the treatments (nusinersen and risdiplam) for symptomatic and presymptomatic use in SMA currently in the NHS, there could potentially be restrictions on these treatments. As such, a scenario in which only Zolgensma is available (i.e. risdiplam and nusinersen are not approved) was also evaluated, as Zolgensma is the only NICE approved treatment in England currently. In this analysis, patients with 2 and 3 SMN2 copies will receive Zolgesma while all other patients with higher SMN2 copy numbers will receive BSC. Similarly, patients with Type 1 SMA receive Zolgensma, while all other patients with different SMA types will receive BSC.

Base case analysis using all available treatments assuming discounts

This analysis used treatments currently eligible for the different SMN2 copies (1, 2, 3, 4, 5+) and SMA types (0, 1, 2, 3, 4) according to the proportions of patients receiving the different treatments as shown in Table 7. In addition, given all these treatments are under confidential discounts, analyses showing what happens when discounts are applied were also performed. Since the real discount of these drugs to the NHS are unknown, a 30% discount for Zolgensma and 90% discount for risdiplam and nusinersen was assumed.

Base case analysis using only zolgensma assuming discount

This analysis evaluated a scenario in which only Zolgensma is available (i.e. risdiplam and nusinersen are not approved) and a 30% discount is assumed for Zolgensma. In this analysis,

patients with 2 and 3 SMN2 copies will receive Zolgensma while all other patients with higher SMN2 copy numbers will receive BSC. Similarly, patients with Type 1 SMA receive Zolgensma, while all other patients with different SMA types will receive BSC.

Sensitivity analyses

The model has the capability for conducting one-way and probabilistic sensitivity analyses, and scenario analysis. Scenario analyses were conducted to identify the impact of parameter uncertainty and key drivers of model outcomes. Probabilistic sensitivity analyses were performed by jointly varying all model parameters over the minimum numbers of simulations necessary to achieve statistical convergence, then calculating 95% credible range estimates for each model outcome based on the results. To account for non-linearities amongst the model inputs, probabilistic sensitivity analysis was undertaken using appropriate distributions to represent the uncertainty in the data inputs.

Results

The results presented in the next sections (unless stated otherwise) refer to the base case analysis using the treatments currently eligible and using list prices. Table 7 presents the treatment mix describing the proportions of patients receiving the different treatments (Zolgensma, Spinraza, Risdiplam or BSC), presymptomatically and symptomatically.

Newborns in the UK

Using an annual cohort of 600,000 newborns in the UK, and an incidence rate of 1 in 8200 for SMA results in 73.17 cases of SMA, with the rest of the population (599,926.83) assumed to be general population. The results presented in this section focus only on the population with SMA.

As mentioned in Model Specification Section, in line with typical health economic practice, a (hypothetical) no-screening plus no treatment/BSC scenario was included as comparator. This is referred as BSC arm of the model, and in this it was assumed that the SMA patients would receive BSC (i.e. not pharmacological treatment). In this arm, it was assumed that all 73.17 cases of SMA would be diagnosed symptomatically and would receive BSC.

In the No NBS screening arm of the model, a small proportion (1%) were assumed to be detected presymptomatically via family history with the rest diagnosed symptomatically. This resulted in 0.73 cases of SMA detected presymptomatically with the rest of 72.44 cases detected symptomatically and receiving pharmacological treatment.

In the NBS screening arm of the model, most of the cases were detected presymptomatically with a small proportion of patients missed and diagnosed symptomatically. The model uses 99.9% sensitivity and specificity for the initial PCR test, and assumes 100% specificity after confirmatory testing (as any false positives would be identified as not having SMA during the genetic testing). Note that the initial PCR test will not detect patients with other variants (i.e. the 5% of patients who do not have homozygous deletions in SMN1), as such the 99.9% sensitivity for the initial PCR test is for the rest of the patients. This resulted in 69.44 cases of SMA detected presymptomatically with the rest of 3.73 cases detected symptomatically.

Table 21. Patients identified symptomatically and presymptomatically in different arms

	Patients diagnosed presymptomatically	**Patients diagnosed symptomatically**
BSC*		73.17
No NBS	0.73	72.44
NBS	69.44	3.73

*assuming no screening and BSC for all patients with SMA

The proportions of the different SMA types (for those detected symptomatically) and SMN2 copy numbers (for those detected presymptomatically) in the No NBS screening arm and NBS screening arm respectively are as presented in Table 22 and Figure 4 below. In the No NBS screening arm, almost all patients are detected symptomatically and most of them have SMA Types 1 and 2. In the NBS screening arm, most patients are detected presymptomatically and most of them have 2, 3 or 4 SMN2 copy numbers.

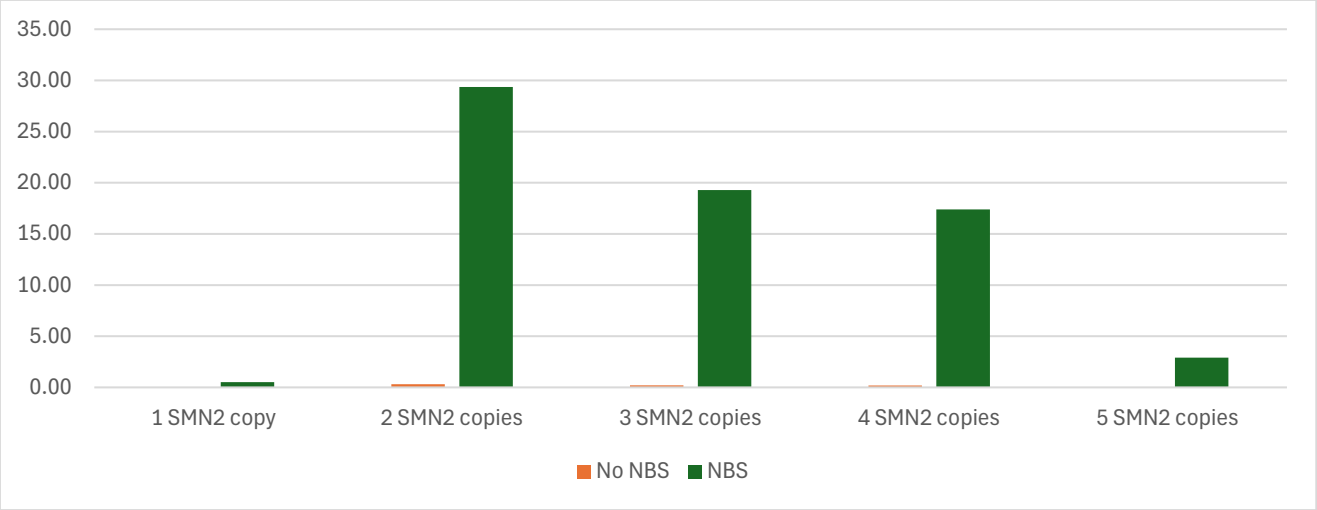
Table 22. Patients identified by SMA type and SMN2 copy number

No NBS screening arm	**Patients diagnosed via family history**				
	0.73				
	Patients by SMN2 copies				
	1 SMN2 copy	2 SMN2 copies	3 SMN2 copies	4 SMN2 copies	5 SMN2 copies
	0.01	0.31	0.20	0.18	0.03
	Patients diagnosed symptomatically				
	72.44				
	Patients by SMA type				
	SMA Type 0	SMA Type 1	SMA Type 2	SMA Type 3	SMA Type 4
	0.53	39.91	19.96	8.95	3.09
NBS screening arm	**Patients diagnosed presymptomatically**				
	69.44				
	Patients by SMN2 copies				
	1 SMN2 copy	2 SMN2 copies	3 SMN2 copies	4 SMN2 copies	5 SMN2 copies
	0.51	29.36	19.28	17.39	2.91
	Patients diagnosed symptomatically				
	3.73				
	Patients by SMA type				

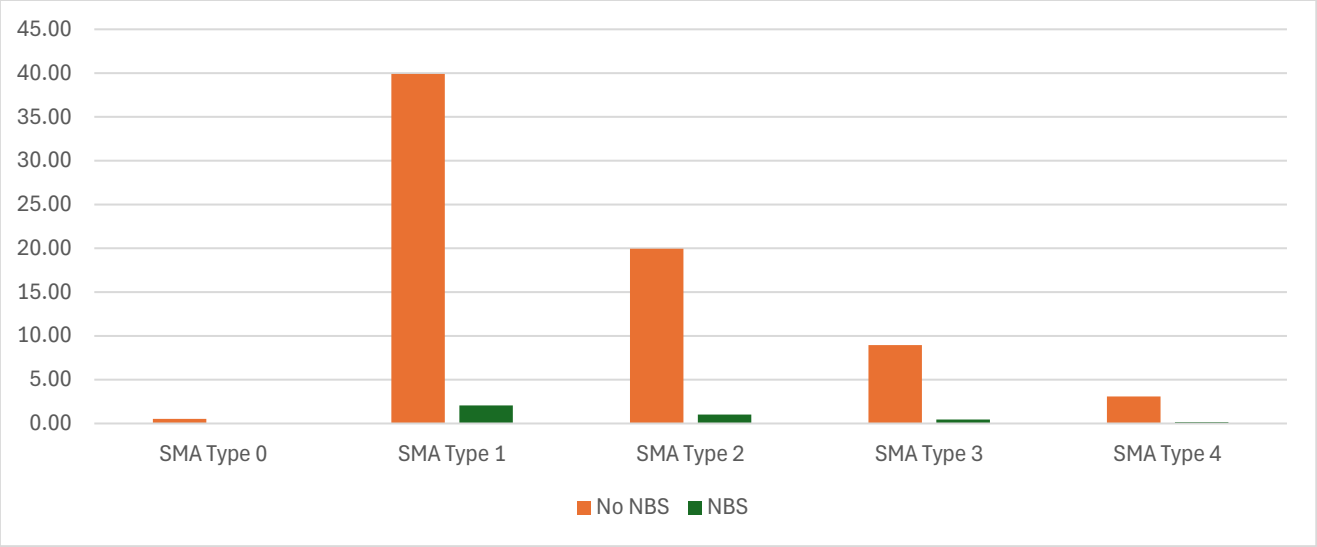
	SMA Type 0	SMA Type 1	SMA Type 2	SMA Type 3	SMA Type 4
	0.03	2.05	1.03	0.46	0.16

Figure 4. Split of patients identified presymptomatically and symptomatically

4a: Patients identified presymptomatically



4b: Patients identified symptomatically



In the No NBS screening arm of the model, only 0.73 cases of SMA are detected presymptomatically while 72.44 cases of SMA are detected symptomatically. The split by SMN2 copy number is similar across both arms as it is based on same epidemiological data (see Table 4).

In the NBS screening arm of the model, 69.44 cases are detected presymptomatically while 3.73 cases are detected symptomatically. The split by SMA type is similar across both arms as it is based on same epidemiological data (see Table 6).

Outcomes at the end of three years

The outcomes presented here are based on the proportions of patients receiving the different treatments (Zolgensma, Spinraza, Risdiplam or BSC) presymptomatically and symptomatically as presented in Table 7, according to the number of SMN2 copies (1, 2, 3, 4, 5+) and the different SMA types (0, 1, 2, 3, 4).

The effectiveness of treatment in both arms of the model (i.e. NBS screening arm and no NBS screening arm) is captured in terms of the motor function milestones achieved. The data from clinical studies on motor function milestones achieved over different time points is input into the model for each of the three treatments (Zolgensma, Spinraza and Risdiplam) as well as best supportive care for different SMN2 copies (1, 2, 3, 4, 5+) and by SMA types (0, 1, 2, 3, 4).

Table 23 presents the patients in different health states in the different arms at the end of the 3 years. In the BSC arm, as the patients are detected symptomatically and only receive BSC (i.e. no pharmacological treatment), the outcomes at the end of the 3 years suggest that there are many deaths and patients on permanent ventilation (PV).

In the No NBS screening arm, where patients are detected symptomatically and receive pharmacological treatment, the number of deaths and patients on PV are reduced substantially but most of the patients are in the sitting health state with only a few patients achieving walking with assistance or BRND.

In the NBS screening arm, where most patients receive pharmacological treatment presymptomatically, the number of deaths and patients on PV and patients in sitting health state are further reduced with most of the patients achieving BRND.

Table 23. Patients by health state at the end of the three years

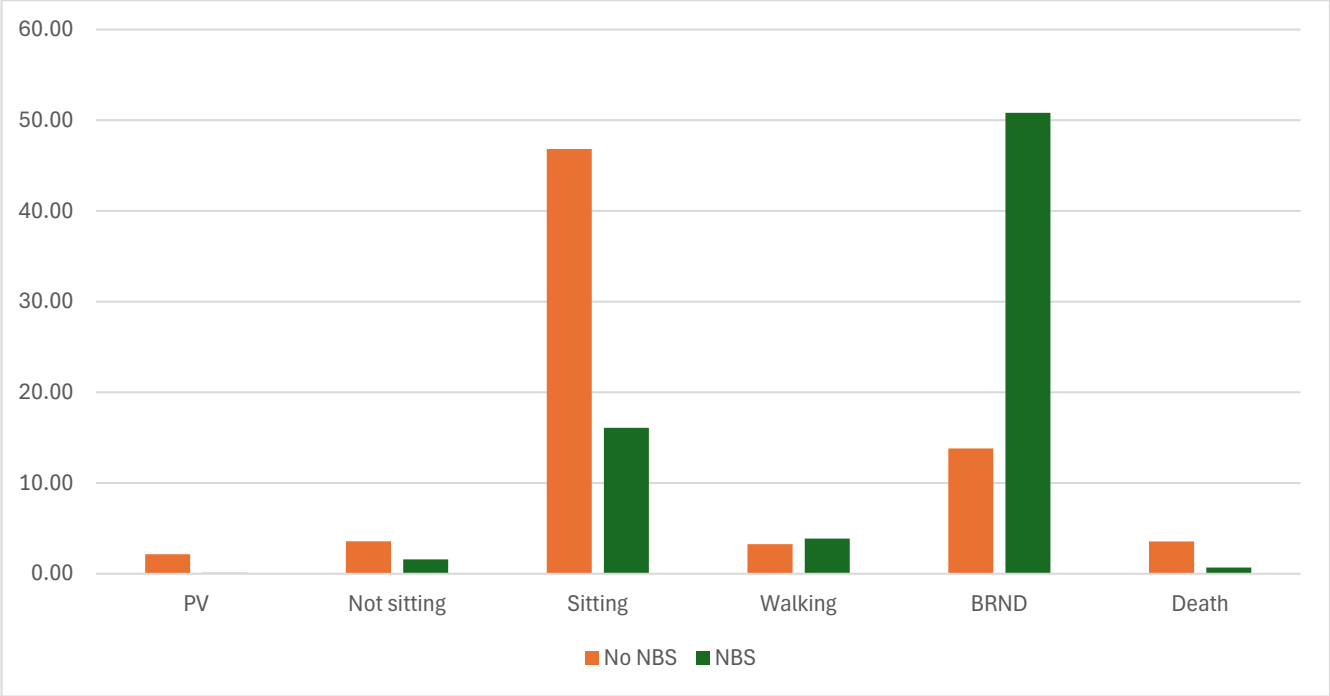
	PV	**Not sitting**	**Sitting**	**Walking with assistance**	**BRND**	**Death**
BSC	10.54	0.62	20.16	9.04	3.12	29.69
No NBS	2.14	3.58	46.82	3.25	13.81	3.56
NBS	0.11	1.58	16.10	3.88	50.82	0.69

*PV: permanent ventilation, BRND: Broad Range of Normal Development

The comparison between No NBS screening arm and NBS screening arm at the end of the 3 years is presented in Figure 5 below. This suggests that compared with current practice (i.e.

assuming all 3 drugs are available), NBS would prevent 2 cases requiring permanent ventilation, around 3 early deaths, and about 30 cases being confined to a sitting state. NBS screening also enables about 37 more cases to live a broadly normal life. However, NBS screening will identify around 3 cases with 5 SMN2 copies, those who will not be affected until adulthood if at all, and this may be detrimental to their health and wellbeing.

Figure 5. Patients at the end of 3 years in the No NBS screening arm and NBS screening arm



Long-term outcomes

The model assumes that the motor function milestones achieved at the end of the follow up are sustained until death and the mortality in the long-term is modelled using survival curves for each of the motor function milestones based on data from published literature (see Table 14).

Figure 6 below presents the time spent in different health states in the BSC, No NBS screening and NBS screening arms.

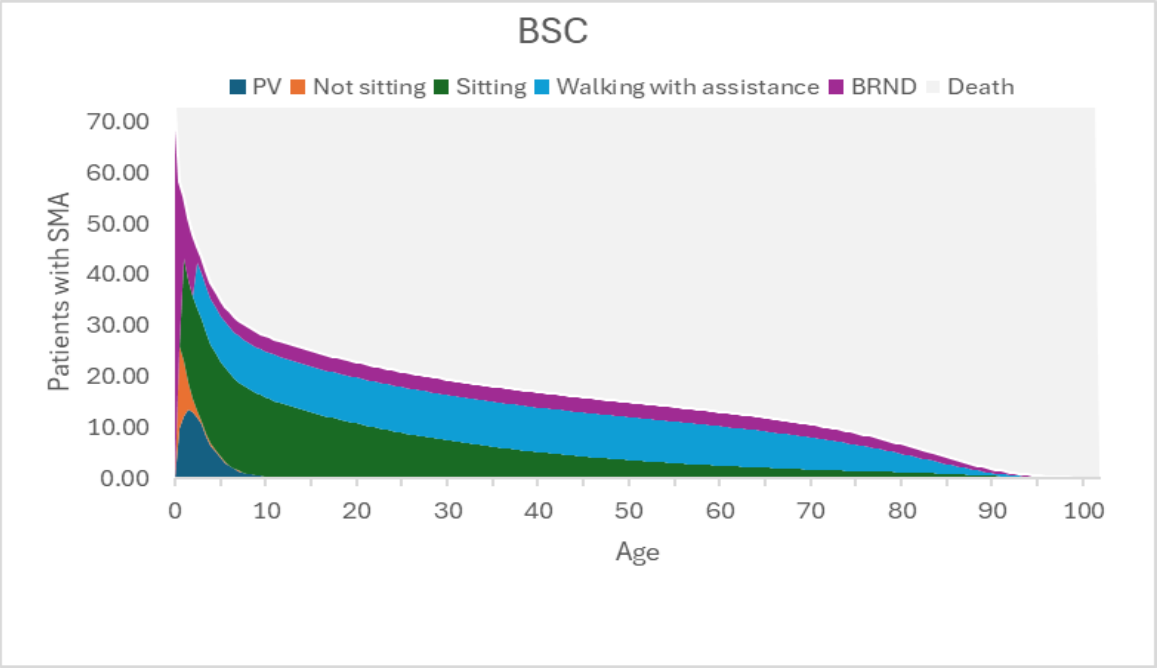
In the BSC arm, the outcomes at the end of the 3 years suggest that there are many deaths and patients on PV with some patients in sitting health state and few in the 'walking with assistance' health state. The lower survival of patients in PV and sitting health states is reflected in the long-term outcomes of patients in BSC.

In the No NBS screening arm, most of the patients are in the sitting health state and some in the BRND state, and only a few patients in the walking with assistance state. The survival in the No NBS screening arm is higher than that in the BSC arm due to lower short-term deaths and fewer patients in PV, but the lower survival of patients in sitting health states is reflected in long-term outcomes of patients in No NBS screening arm.

In the NBS screening arm, the number of deaths and patients on PV and patients in sitting health state are further reduced with most of the patients achieving BRND. The survival in the N BS screening arm is much higher than that in the No NBS screening arm due to lower short-term deaths, fewer patients in PV, and fewer patients in sitting health states. Most of the patients in the NBS screening arm are in the BRND state (which has survival of general population) and this is reflected in better long-term outcomes of patients in NBS screening arm.

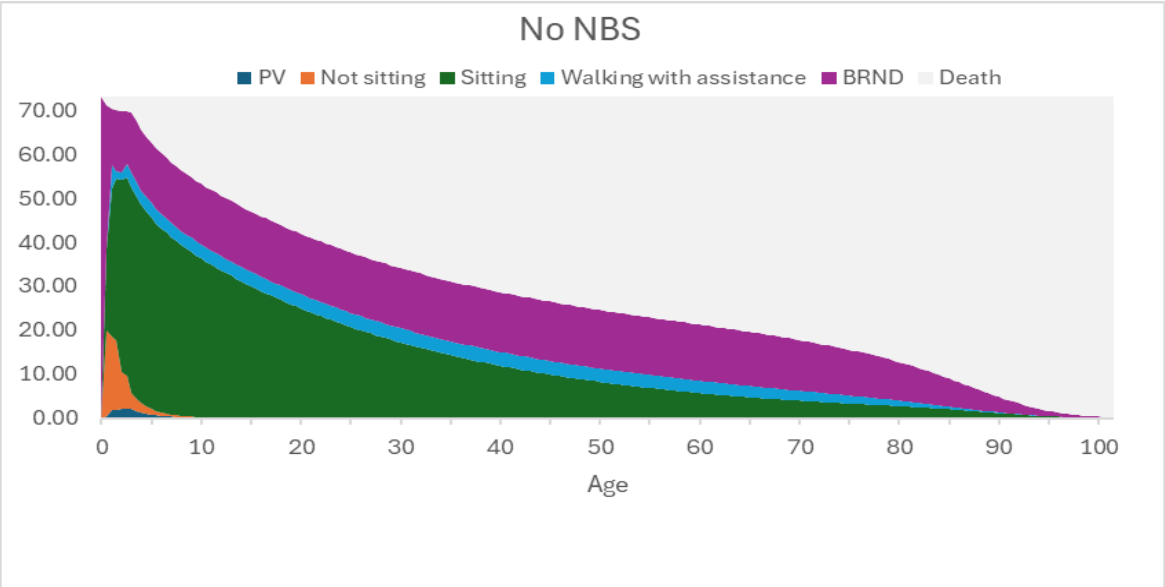
Figure 6. Time spent in different health states in the different arms

6a: BSC arm



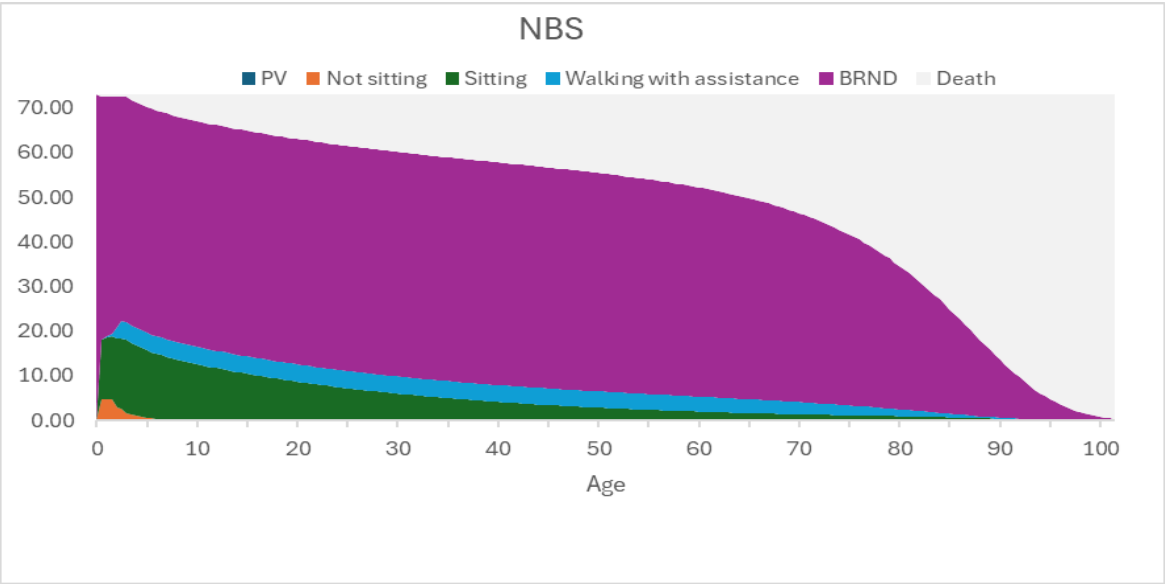
*Time spent in the different health states by the 73.17 patients with SMA. In this BSC arm, there are many deaths, and patients on PV with some patients in sitting health state and few in the walking with assistance health state. The lower survival of patients in PV and sitting health states is reflected in the long-term outcomes of patients in BSC.

6b: No NBS screening arm



*Time spent in the different health states by the 73.17 patients with SMA. In this No NBS screening arm, most of the patients are in the sitting health state and some in the BRND state, and only a few patients in the walking with assistance state. The survival in the No NBS screening arm is higher than that in the BSC arm due to lower short-term deaths and fewer patients in PV, but the lower survival of patients in sitting health states is reflected in long-term outcomes of patients in No NBS screening arm.

6c: NBS screening arm



*Time spent in the different health states by the 73.17 patients with SMA. In this NBS screening arm, the number of deaths and patients on PV and patients in sitting health state are further reduced with most of the patients achieving BRND. The survival in the NBS screening arm is much higher than that in the No NBS screening arm due to lower short-term deaths, fewer patients in PV, and fewer patients in sitting health states. Most of the patients in the NBS screening arm are in the BRND state (which has survival of general population) and this is reflected in better long-term outcomes of patients in NBS screening arm.

Breakdown of costs and QALYs by health state

Table 24 presents the breakdown of discounted lifetime costs and QALYs by health states in the No NBS screening and NBS screening arms, using 3.5% discount rate for both costs and outcomes.

Table 24. Breakdown of discounted lifetime costs and outcomes by health state, using list prices (using 3.5% discount rate for both costs and outcomes)

No NBS						
	Ventilated	**Not sitting**	**Sitting**	**Walking with assistance**	**BRND**	**Total**
Life Years	7.95	39.01	678.91	82.48	429.19	**1237.55**
QALYs	1.51	7.41	400.10	63.53	373.21	**845.75**
Diagnostic costs						**£ 182,628**
Nusinersen costs	£ -	£ 400,949	£ 8,226,507	£ 2,132,659	£ 5,278,848	**£ 16,038,963**
Zolgensma costs	£ -	£ -	£ -	£ -	£ 61,807,545	**£ 61,807,545**
Risdiplam costs	£ -	£ 415,886	£ 53,290,686	£ 16,096,298	£ 46,632,843	**£ 116,435,713**
Health state costs	£ 2,061,509	£ 5,782,551	£ 46,378,004	£ 1,795,395	£ 858,379	**£ 56,875,837**
NBS						
	Ventilated	**Not sitting**	**Sitting**	**Walking with assistance**	**BRND**	**Total**
Life Years	0.41	12.27	240.89	95.88	1402.64	**1752.09**
QALYs	0.08	2.33	142.02	73.76	1214.53	**1432.71**
Diagnostic costs						**£ 6,690,148**
Nusinersen costs	£ -	£ 195,078	£ 2,501,309	£ 131,819	£ 16,981,897	**£ 19,810,103**
Zolgensma costs	£ -	£ -	£ -	£ -	£ 78,130,790	**£ 78,130,790**
Risdiplam costs	£ -	£ 190,549	£ 6,437,256	£ 845,059	£ 110,264,471	**£ 117,737,334**
Health state costs	£ 106,095	£ 1,817,912	£ 16,455,990	£ 2,087,121	£ 2,805,281	**£ 23,272,399**

The life years (LYs) and QALYs are higher in the NBS screening arm compared to the No NBS screening arm. This is because most of the patients in the NBS screening arm are in the BRND

state (which has survival of general population) and this is reflected in better long-term outcomes of patients in NBS screening arm. In the No NBS screening arm, most of the patients are in the sitting health state but the LYs and QALYs accrued are lower due to the lower survival of patients in the sitting health state.

Although the screening costs and treatment costs are higher in the NBS screening arm, the health state costs are much lower compared to the No NBS screening arm. This is because most of the patients in the NBS screening arm are in the BRND state (which has much lower costs compared to other health states) and this is reflected in lower overall health state costs of patients in NBS screening arm. In the No NBS screening arm, most of the patients are in the sitting health state which has high costs (see Table 20) which results in much higher overall health state costs in the No NBS screening arm.

In this analysis, roughly 9 additional patients receive Zolgensma in the NBS screening arm (24.96 patients diagnosed presymptomatically with 2 SMN2 copies, 16.38 with 3 SMN2 copies and 1.74 patients diagnosed symptomatically with SMA Type 1) compared to the No NBS screening arm (roughly 34 patients with SMA Type 1).

Cost-effectiveness results

Results of base case analysis

As discussed earlier, given the uncertainty in the reimbursement status of the treatments in the future and the lack of “actual” prices, the base case analyses included 4 different analyses as described below. All the analyses were performed using 3.5% discount rates for costs and outcomes.

Results of Base case analysis using all available treatments and list prices

Table 25 presents the cost-effectiveness results of the base case analysis i.e. using all the treatments currently eligible (Table 7 presents the treatment mix describing the proportions of patients receiving the different treatments) and using list prices.

Table 25. Cost-effectiveness results using all available treatments and list prices

	Screening/ Diagnosis Costs	Treatment Costs	Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
							Cost/QALY Gained	Cost/LY Gained
NBS screening	£ 6,690,148	£ 215,678,227	£ 23,272,399	£ 245,640,775	1432.71	1752.09	-£ 9,711	-£ 11,078
No NBS screening	£ 182,628	£ 194,282,221	£ 56,875,837	£ 251,340,686	845.75	1237.55	£ 606,516	£ 426,163

BSC	£ 182,927	£ -	£ 40,472,763	£ 40,655,689	498.38	743.17		

Table 25 suggests higher total QALYs and lower total costs in the NBS screening arm compared to the No NBS screening arm, resulting in NBS screening dominating the No NBS screening arm. However, it should be noted that No NBS screening is not cost-effective compared to BSC with an incremental cost-effectiveness ratio (ICER) of £606,516/QALY. The ICER of NBS screening compared to BSC is £219,393/QALY, also suggesting that NBS screening is not cost-effective when compared to BSC.

Results of Base case analysis using all available treatments assuming discounts

This analysis used treatments all currently eligible (Table 7 presents the treatment mix describing the proportions of patients receiving the different treatments) and using 30% discount for Zolgensma and 90% discount for risdiplam and nusinersen. Table 26 presents the cost-effectiveness results of this analysis.

Table 26 suggests higher total QALYs and lower total costs in the NBS screening arm compared to the No NBS screening arm, resulting in NBS screening dominating the No NBS screening arm. However, it should be noted that No NBS screening is not cost-effective compared to BSC with an incremental cost-effectiveness ratio (ICER) of £210,930/QALY. The ICER of NBS screening compared to BSC is £62,217/QALY, which could be considered cost-effective at thresholds of £100,000/QALY used for NICE highly specialised technologies (HSTs) but not cost-effective at the typical NICE thresholds of £20,000 to £30,000/QALY.

Table 26. Cost-effectiveness results using all available treatments and with price discounts

	Screening/ Diagnosis Costs	**Treatment Costs**	**Health Care Costs**	**Total Costs**	**QALYs**	**LYs**	**Incremental Results**	
							Cost/QALY Gained	**Cost/LY Gained**
NBS screening	£ 6,690,148	£ 68,824,724	£ 23,272,399	£ 98,787,272	1432.71	1752.09	-£ 25,793	-£ 29,423
No NBS screening	£ 182,628	£ 56,868,003	£ 56,875,837	£ 113,926,468	845.75	1237.55	£ 210,930	£ 148,209
BSC	£ 182,927	£ -	£ 40,472,763	£ 40,655,689	498.38	743.17		

Table 27 presents the breakdown of lifetime costs and outcomes with treatment discounts. The outcomes (LYs and QALYs) as well as diagnostic and health state costs remain the same as previous analysis (Table 24). However, the treatment costs in this analysis are lower due to the price discounts applied.

Table 27. Breakdown of lifetime costs and outcomes by health state, using discounts for treatments

No NBS screening						
	Ventilated	**Not sitting**	**Sitting**	**Walking with assistance**	**BRND**	**Total**
Life Years	7.95	39.01	678.91	82.48	429.19	**1237.55**
QALYs	1.51	7.41	400.10	63.53	373.21	**845.75**
Diagnostic costs						**£ 182,628**
Nusinersen costs	£ -	£ 47,170	£ 946,366	£ 241,111	£ 594,329	**£ 1,828,977**
Zolgensma costs	£ -	£ -	£ -	£ -	£ 43,301,366	**£ 43,301,366**
Risdiplam costs	£ -	£ 44,153	£ 5,381,279	£ 1,621,448	£ 4,690,781	**£ 11,737,661**
Health state costs	£ 2,061,509	£ 5,782,551	£ 46,378,004	£ 1,795,395	£ 858,379	**£ 56,875,837**
NBS screening						
	Ventilated	**Not sitting**	**Sitting**	**Walking with assistance**	**BRND**	**Total**
Life Years	0.41	12.27	240.89	95.88	1402.64	**1752.09**
QALYs	0.08	2.33	142.02	73.76	1214.53	**1432.71**
Diagnostic costs						**£ 6,690,148**
Nusinersen costs	£ -	£ 22,950	£ 287,784	£ 15,004	£ 1,921,615	**£ 2,247,354**
Zolgensma costs	£ -	£ -	£ -	£ -	£ 54,737,167	**£ 54,737,167**
Risdiplam costs	£ -	£ 19,367	£ 648,570	£ 85,137	£ 11,087,128	**£ 11,840,203**
Health state costs	£ 106,095	£ 1,817,912	£ 16,455,990	£ 2,087,121	£ 2,805,281	**£ 23,272,399**

Results of Base case analysis using zolgensma only, and at list price

A scenario in which only Zolgensma is available (i.e. risdiplam and nusinersen are not approved) was also evaluated, as Zolgensma is the only NICE approved treatment in England currently. In this analysis, patients with 2 and 3 SMN2 copies will receive Zolgesma while all other patients with higher SMN2 copy numbers will receive BSC. Similarly, patients with Type 1 SMA receive Zolgensma, while all other patients with different SMA types will receive BSC.

In this analysis, roughly 10 additional patients receive Zolgensma in the NBS sceening arm (29.36 patients diagnosed presymptomatically with 2 SMN2 copies, 19.28 with 3 SMN2 copies and 2.05 patients diagnosed symptomatically with SMA Type 1) compared to the No NBS screening arm (roughly 40 patients with SMA Type 1).

Table 28 presents the cost-effectiveness results of this analysis. Table 28 suggests higher total QALYs and lower total costs in the NBS screening arm compared to the No NBS screening arm, resulting in NBS screening dominating the No NBS screening arm. However, it should be noted

that No NBS screening is not cost-effective compared to BSC with an (ICER of £309,367/QALY). The ICER of NBS screening compared to BSC is £99,197/QALY, which is just cost-effective at threshold of £100,000/QALY used for NICE HSTs but not cost-effective at the typical NICE thresholds of £20,000 to £30,000/QALY.

Table 28. Cost-effectiveness results using Zolgensma only, and using list price

	Screening/ Diagnosis Costs	**Treatment Costs**	**Health Care Costs**	**Total Costs**	**QALYs**	**LYs**	**Incremental Results**	
							Cost/QALY Gained	**Cost/LY Gained**
NBS screening	£ 6,690,148	£ 91,918,576	£ 30,522,146	£ 129,130,870	1390.29	1742.25	-£ 12,659	-£ 14,361
No NBS screening	£ 182,628	£ 72,714,759	£ 63,602,370	£ 136,499,757	808.18	1229.14	£ 309,367	£ 197,224
BSC	£ 182,927	£ -	£ 40,472,763	£ 40,655,689	498.38	743.17		

Table 29 presents the breakdown of lifetime costs and QALYs by health states in the No NBS screening and NBS screening arms. The life years (LYs) and QALYs are higher in the NBS screening arm compared to the No NBS screening arm. This is because most of the patients in the NBS screening arm are in the BRND state (which has survival of general population) and this is reflected in better long-term outcomes of patients in NBS screening arm. In the No NBS screening arm, most of the patients are in the sitting health state but the LYs and QALYs accrued are lower due to the lower survival of patients in sitting health states.

Although the screening costs and treatment costs are higher in the NBS screening arm, the health state costs are much lower compared to the No NBS screening arm. This is because most of the patients in the NBS screening arm screening are in the BRND state (which has much lower costs compared to other health states) and this is reflected in lower overall health state costs of patients in NBS screening arm. In the No NBS screening arm, most of the patients are in the sitting health state which has high costs (see Table 20) which results in much higher overall health state costs in the No NBS screening arm.

Table 29. Breakdown of lifetime costs and outcomes by health state, using Zolgensma only and at list price

No NBS screening						
	Ventilated	**Not sitting**	**Sitting**	**Walking with assistance**	**BRND**	**Total**
Life Years	5.42	38.25	750.87	220.77	213.82	**1229.14**
QALYs	1.03	7.26	442.50	169.72	187.67	**808.18**
Diagnostic costs						**£ 182,628**

Nusinersen costs	£ -	£ -	£ -	£ -	£ -	**£ -**
Zolgensma costs	£ -	£ -	£ -	£ -	£ 72,714,759	**£ 72,714,759**
Risdiplam costs	£ -	£ -	£ -	£ -	£ -	**£ -**
Health state costs	£ 1,406,428	£ 5,669,389	£ 51,293,124	£ 4,805,783	£ 427,645	**£ 63,602,370**
NBS screening						
	Ventilated	**Not sitting**	**Sitting**	**Walking with assistance**	**BRND**	**Total**
Life Years	0.28	11.35	248.89	445.22	1036.50	**1742.25**
QALYs	0.05	2.16	146.72	342.29	899.07	**1390.29**
Diagnostic costs						**£ 6,690,148**
Nusinersen costs	£ -	£ -	£ -	£ -	£ -	**£ -**
Zolgensma costs	£ -	£ -	£ -	£ -	£ 91,918,576	**£ 91,918,576**
Risdiplam costs	£ -	£ -	£ -	£ -	£ -	**£ -**
Health state costs	£ 72,381	£ 1,682,765	£ 17,002,363	£ 9,691,639	£ 2,072,997	**£ 30,522,146**

Results of Base case analysis using zolgensma only, assuming 30% discount

This analysis evaluated a scenario in which only Zolgensma is available (i.e. risdiplam and nusinersen are not approved) and a 30% discount is assumed for Zolgensma. In this analysis, patients with 2 and 3 SMN2 copies will receive Zolgensma while all other patients with higher SMN2 copy numbers will receive BSC. Similarly, patients with Type 1 SMA receive Zolgensma, while all other patients with different SMA types will receive BSC.

Table 30 presents the cost-effectiveness results of this analysis. Table 30 suggests higher total QALYs and lower total costs in the NBS screening arm compared to the No NBS screening arm, resulting in NBS screening dominating the No NBS screening arm. However, it should be noted that No NBS screening is not cost-effective compared to BSC with an (ICER of £239,091/QALY. The ICER of NBS screening compared to BSC is £68,340/QALY, which could be considered cost-effective at threshold of £100,000/QALY used for NICE HSTs but not cost-effective at the typical NICE thresholds of £20,000 to £30,000/QALY.

Table 30. Cost-effectiveness results using Zolgensma only, at 30% discount

	Screening/ Diagnosis Costs	**Treatment Costs**	**Health Care Costs**	**Total Costs**	**QALYs**	**LYs**	**Incremental Results**	
							Cost/QALY Gained	**Cost/LY Gained**
NBS screening	£ 6,690,148	£ 64,396,667	£ 30,522,146	£ 101,608,961	1390.29	1742.25	-£ 22,537	-£ 25,567

No NBS screening	£ 182,628	£ 50,942,783	£ 63,602,370	£ 114,727,782	808.18	1229.14	£ 239,091	£ 152,423
BSC	£ 182,927	£ -	£ 40,472,763	£ 40,655,689	498.38	743.17		

Table 31 presents the breakdown of lifetime costs and outcomes with treatment discount of 30% for Zolgensma. The outcomes (LYs and QALYs) as well as diagnostic and health state costs remain the same as previous analysis (Table 29). However, the zolgensma treatment costs in this analysis are lower due to the discounts applied.

Table 31. Breakdown of lifetime costs and outcomes by health state, using Zolgensma only and using 30% discount

No NBS screening						
	Ventilated	**Not sitting**	**Sitting**	**Walking with assistance**	**BRND**	**Total**
Life Years	5.42	38.25	750.87	220.77	213.82	**1229.14**
QALYs	1.03	7.26	442.50	169.72	187.67	**808.18**
Diagnostic costs						**£ 182,628**
Nusinersen costs	£ -	£ -	£ -	£ -	£ -	**£ -**
Zolgensma costs	£ -	£ -	£ -	£ -	£ 50,942,783	**£ 50,942,783**
Risdiplam costs	£ -	£ -	£ -	£ -	£ -	**£ -**
Health state costs	£ 1,406,428	£ 5,669,389	£ 51,293,124	£ 4,805,783	£ 427,645	**£ 63,602,370**
NBS screening						
	Ventilated	**Not sitting**	**Sitting**	**Walking with assistance**	**BRND**	**Total**
Life Years	0.28	11.35	248.89	445.22	1036.50	**1742.25**
QALYs	0.05	2.16	146.72	342.29	899.07	**1390.29**
Diagnostic costs						**£ 6,690,148**
Nusinersen costs	£ -	£ -	£ -	£ -	£ -	**£ -**
Zolgensma costs	£ -	£ -	£ -	£ -	£ 64,396,667	**£ 64,396,667**
Risdiplam costs	£ -	£ -	£ -	£ -	£ -	**£ -**
Health state costs	£ 72,381	£ 1,682,765	£ 17,002,363	£ 9,691,639	£ 2,072,997	**£ 30,522,146**

Summary of Base case analysis results

Table 32 presents the cost-effectiveness results of all four base case analysis together. In all the base case analyses, NBS screening seems to be cost saving and more effective compared to No NBS screening.

However, comparing across the different base case analyses need to be performed with caution as all the ICERs are negative. The typical rules (e.g. a low ICER being more cost-effective and vice versa) do not apply in the case of negative ICERs.

For instance, in Table 32, in the ICERs describing the cost effectiveness of treatment with Zolgensma comparing 'list price' vs '30% discount': for 'No NBS screening' vs 'BSC', the cost per QALY gained is £309,367 vs £239,091 respectively reflecting the 30% cost reduction of treatment. However, for 'NBS screening' the cost per QALY gained is goes from -£12,659/QALY to -£22,537/QALY which initially seems to suggest that ICER has increased. However, as both the ICERs are negative, in this instance the change in ICER reflects the greater cost savings in the analysis with 30% discount (with same benefits in QALYs) compared to the analysis with the list price. As such, the change in ICER does indeed appear to reflect the reduced cost of treatment, and the cost per QALY with the discount in place is considered better than the analysis with the list price.

Table 32. Summary of Base case Cost-effectiveness results

	Screening/ Diagnosis Costs	**Treatment Costs**	**Health Care Costs**	**Total Costs**	**QALYs**	**LYs**	**Incremental Results**	
							Cost/QALY Gained	**Cost/LY Gained**
Base case analysis using all available treatments and list prices								
NBS screening	£ 6,690,148	£ 215,678,227	£ 23,272,399	£ 245,640,775	1432.71	1752.09	-£ 9,711	-£ 11,078
No NBS screening	£ 182,628	£ 194,282,221	£ 56,875,837	£ 251,340,686	845.75	1237.55	£ 606,516	£ 426,163
BSC	£ 182,927	£ -	£ 40,472,763	£ 40,655,689	498.38	743.17		
Base case analysis using all available treatments assuming discounts								
NBS screening	£ 6,690,148	£ 68,824,724	£ 23,272,399	£ 98,787,272	1432.71	1752.09	-£ 25,793	-£ 29,423
No NBS screening	£ 182,628	£ 56,868,003	£ 56,875,837	£ 113,926,468	845.75	1237.55	£ 210,930	£ 148,209
BSC	£ 182,927	£ -	£ 40,472,763	£ 40,655,689	498.38	743.17		
Base case analysis using zolgensma only, and at list price								
NBS screening	£ 6,690,148	£ 91,918,576	£ 30,522,146	£ 129,130,870	1390.29	1742.25	-£ 12,659	-£ 14,361
No NBS screening	£ 182,628	£ 72,714,759	£ 63,602,370	£ 136,499,757	808.18	1229.14	£ 309,367	£ 197,224

BSC	£ 182,927	£ -	£ 40,472,763	£ 40,655,689	498.38	743.17		
Base case analysis using zolgensma only, and at 30% discount								
NBS screening	£ 6,690,148	£ 64,396,667	£ 30,522,146	£ 101,608,961	1390.29	1742.25	-£ 22,537	-£ 25,567
No NBS screening	£ 182,628	£ 50,942,783	£ 63,602,370	£ 114,727,782	808.18	1229.14	£ 239,091	£ 152,423
BSC	£ 182,927	£ -	£ 40,472,763	£ 40,655,689	498.38	743.17		

Results of scenario analysis

As discussed earlier, given the uncertainty in the reimbursement status of the treatments in the future and the lack of "actual" prices, the scenario analyses included 4 different analyses (as described in section above). All the analyses were performed using 3.5% discount rates for costs and outcomes, except for the scenario using different discount rates (i.e. 1.5% discount rate for health benefits).

Results of scenario analyses incorporating treatment waning

Table 33 presents the cost-effectiveness results of scenario analyses incorporating treatment waning of presymptomatic treatment in the NBS screening arm. In this scenario, it was assumed that at the end of three years, half of the patients in BRND would move to 'walking with assistance' health state and the same proportion of patients would move from 'walking with assistance' health state to 'sitting' health state. This loss of milestones was only applied to patients receiving presymptomatic treatment in the NBS screening arm. Even in this pessimistic scenario, NBS screening is cost-effective or cost saving as seen in Table 33 below.

Table 33. Results of scenario analyses incorporating treatment waning

	Screening/ Diagnosis Costs	**Treatment Costs**	**Health Care Costs**	**Total Costs**	**QALYs**	**LYs**	**Incremental Results**	
							Cost/QALY Gained	**Cost/LY Gained**
Analysis using all available treatments and list prices								
NBS screening	£ 6,690,148	£ 214,242,956	£ 34,447,146	£ 255,380,251	1358.77	1726.75	£ 7,874	£ 8,257
No NBS screening	£ 182,628	£ 194,282,221	£ 56,875,837	£ 251,340,686	845.75	1237.55	£ 606,516	£ 426,163
BSC	£ 182,927	£ -	£ 40,472,763	£ 40,655,689	498.38	743.17		
Analysis using all available treatments assuming discounts								

NBS screening	£ 6,690,148	£ 68,679,135	£ 34,447,146	£ 109,816,429	1358.77	1726.75	-£ 8,011	-£ 8,402
No NBS screening	£ 182,628	£ 56,868,003	£ 56,875,837	£ 113,926,468	845.75	1237.55	£ 210,930	£ 148,209
BSC	£ 182,927	£ -	£ 40,472,763	£ 40,655,689	498.38	743.17		
Analysis using zolgensma only, and at list price								
NBS screening	£ 6,690,148	£ 91,918,576	£ 91,222,886	£ 189,831,611	3466.95	4629.47	-£ 3,166	-£ 2,770
No NBS screening	£ 182,628	£ 72,714,759	£ 122,418,764	£ 195,316,151	1734.67	2649.58	£ 195,937	£ 121,882
BSC	£ 182,927	£ -	£ 70,540,994	£ 70,723,921	1098.79	1627.34		
Analysis using zolgensma only, and at 30% discount								
NBS screening	£ 6,690,148	£ 64,396,667	£ 38,049,321	£ 109,136,137	1335.81	1719.49	-£ 10,598	-£ 11,403
No NBS screening	£ 182,628	£ 50,942,783	£ 63,602,370	£ 114,727,782	808.18	1229.14	£ 239,091	£ 152,423
BSC	£ 182,927	£ -	£ 40,472,763	£ 40,655,689	498.38	743.17		

Results of scenario analyses incorporating lower life expectancy

Table 34 presents the cost-effectiveness results of scenario analyses assuming lower life expectancy of 50 years in patients with 'walking with assistance' and 60 years for BRND. In all these scenario analyses, NBS screening seems to be cost saving and more effective compared to No NBS screening.

Table 34. Results of scenario analyses incorporating lower life expectancy

	Screening/ Diagnosis Costs	**Treatment Costs**	**Health Care Costs**	**Total Costs**	**QALYs**	**LYs**	**Incremental Results**	
							Cost/QALY Gained	**Cost/LY Gained**
Analysis using all available treatments and list prices								
NBS screening	£ 6,690,148	£ 198,871,835	£ 22,836,973	£ 228,398,957	1300.62	1581.23	-£ 29,713	-£ 37,256
No NBS screening	£ 182,628	£ 186,158,094	£ 56,699,207	£ 243,039,929	807.87	1188.24	£ 623,667	£ 434,590

BSC	£ 182,927	£ -	£ 40,213,758	£ 40,396,684	482.95	721.95		
Analysis using all available treatments assuming discounts								
NBS screening	£ 6,690,148	£ 67,119,781	£ 22,836,973	£ 96,646,903	1300.62	1581.23	-£ 33,040	-£ 41,427
No NBS screening	£ 182,628	£ 56,045,257	£ 56,699,207	£ 112,927,092	807.87	1188.24	£ 223,224	£ 155,549
BSC	£ 182,927	£ -	£ 40,213,758	£ 40,396,684	482.95	721.95		
Analysis using zolgensma only, and at list price								
NBS screening	£ 6,690,148	£ 91,918,576	£ 29,801,316	£ 128,410,041	1284.13	1602.67	-£ 15,746	-£ 19,481
No NBS screening	£ 182,628	£ 72,714,759	£ 63,327,769	£ 136,225,156	787.80	1201.52	£ 314,342	£ 199,824
BSC	£ 182,927	£ -	£ 40,213,758	£ 40,396,684	482.95	721.95		
Analysis using zolgensma only, and at 30% discount								
NBS screening	£ 6,690,148	£ 64,396,667	£ 29,801,316	£ 100,888,132	1284.13	1602.67	-£ 27,331	-£ 33,815
No NBS screening	£ 182,628	£ 50,942,783	£ 63,327,769	£ 114,453,181	787.80	1201.52	£ 242,924	£ 154,425
BSC	£ 182,927	£ -	£ 40,213,758	£ 40,396,684	482.95	721.95		

Results of scenario analyses using alternative utility values

Table 35 presents the cost-effectiveness results using alternative utility values as presented in Table 16. In all the analyses, NBS screening seems to be cost saving and more effective compared to No NBS screening.

Table 35. Cost-effectiveness results of scenario using alternative utility values

	Screening/ Diagnosis Costs	**Treatment Costs**	**Health Care Costs**	**Total Costs**	**QALYs**	**LYs**	**Incremental Results**	
							Cost/QALY Gained	**Cost/LY Gained**
Analysis using all available treatments and list prices								
NBS screening	£ 6,690,148	£ 215,678,227	£ 23,272,399	£ 245,640,775	1396.74	1752.09	-£ 8,840	-£ 11,078

No NBS screening	£ 182,628	£ 194,282,221	£ 56,875,837	£ 251,340,686	751.94	1237.55	£ 699,803	£ 426,163
BSC	£ 182,927	£ -	£ 40,472,763	£ 40,655,689	450.88	743.17		
Analysis using all available treatments assuming discounts								
NBS screening	£ 6,690,148	£ 68,824,724	£ 23,272,399	£ 98,787,272	1396.74	1752.09	-£ 23,479	-£ 29,423
No NBS screening	£ 182,628	£ 56,868,003	£ 56,875,837	£ 113,926,468	751.94	1237.55	£ 243,373	£ 148,209
BSC	£ 182,927	£ -	£ 40,472,763	£ 40,655,689	450.88	743.17		
Analysis using zolgensma only, and at list price								
NBS screening	£ 6,690,148	£ 91,918,576	£ 30,522,146	£ 129,130,870	1339.73	1742.25	-£ 11,503	-£ 14,361
No NBS screening	£ 182,628	£ 72,714,759	£ 63,602,370	£ 136,499,757	699.12	1229.14	£ 386,088	£ 197,224
BSC	£ 182,927	£ -	£ 40,472,763	£ 40,655,689	450.88	743.17		
Analysis using zolgensma only, and at 30% discount								
NBS screening	£ 6,690,148	£ 64,396,667	£ 30,522,146	£ 101,608,961	1339.73	1742.25	-£ 20,479	-£ 25,567
No NBS screening	£ 182,628	£ 50,942,783	£ 63,602,370	£ 114,727,782	699.12	1229.14	£ 298,384	£ 152,423
BSC	£ 182,927	£ -	£ 40,472,763	£ 40,655,689	450.88	743.17		

Results of scenario analyses using alternative health state costs

Table 36 presents the cost-effectiveness results in the scenario where sitting health state costs are assumed to be halved (i.e. £34,156 per year rather than the £68,312 in the base case analyses). In all the analyses, NBS screening seems to be either cost-effective or cost saving and more effective compared to No NBS screening.

Table 36. Cost-effectiveness results of scenario using alternative utility values

	Screening/ Diagnosis Costs	Treatment Costs	Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
							Cost/QALY Gained	Cost/LY Gained
Analysis using all available treatments and list prices								
NBS screening	£ 6,690,148	£ 215,678,227	£ 15,044,404	£ 237,412,780	1432.71	1752.09	£ 15,778	£ 17,999
No NBS screening	£ 182,628	£ 194,282,221	£ 33,686,835	£ 228,151,684	845.75	1237.55	£ 568,670	£ 399,571
BSC	£ 182,927	£ -	£ 30,430,192	£ 30,613,119	498.38	743.17		
Analysis using all available treatments assuming discounts								
NBS screening	£ 6,690,148	£ 68,824,724	£ 15,044,404	£ 90,559,277	1432.71	1752.09	-£ 304	-£ 346
No NBS screening	£ 182,628	£ 56,868,003	£ 33,686,835	£ 90,737,467	845.75	1237.55	£ 173,085	£ 121,617
BSC	£ 182,927	£ -	£ 30,430,192	£ 30,613,119	498.38	743.17		
Analysis using zolgensma only, and at list price								
NBS screening	£ 6,690,148	£ 91,918,576	£ 22,020,964	£ 120,629,688	1390.29	1742.25	£ 16,795	£ 19,053
No NBS screening	£ 182,628	£ 72,714,759	£ 37,955,808	£ 110,853,195	808.18	1229.14	£ 259,000	£ 165,115
BSC	£ 182,927	£ -	£ 30,430,192	£ 30,613,119	498.38	743.17		
Analysis using zolgensma only, and at 30% discount								
NBS screening	£ 6,690,148	£ 64,396,667	£ 22,020,964	£ 93,107,779	1390.29	1742.25	£ 6,917	£ 7,847
No NBS screening	£ 182,628	£ 50,942,783	£ 37,955,808	£ 89,081,219	808.18	1229.14	£ 188,724	£ 120,313
BSC	£ 182,927	£ -	£ 30,430,192	£ 30,613,119	498.38	743.17		

Results of scenario analyses using higher screening costs

Table 37 presents the cost-effectiveness results in the scenario where the NBS screening costs are assumed to be doubled. Note that this is only applied to the initial PCR test (increased to

£14 per test from £7) and the cost of setting up the NBS service (increased to £6 per patient screened from £3 per patient), and not to the confirmatory tests or transport or clinician appointments (all of which remained the same). In all the analyses, NBS screening seems to be either cost-effective or cost saving and more effective compared to No NBS screening.

Table 37. Cost-effectiveness results of scenario using alternative utility values

	Screening/ Diagnosis Costs	Treatment Costs	Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
							Cost/QALY Gained	Cost/LY Gained
Analysis using all available treatments and list prices								
NBS screening	£ 12,690,148	£ 215,678,227	£ 23,272,399	£ 251,640,775	1432.71	1752.09	£ 511	£ 583
No NBS screening	£ 182,628	£ 194,282,221	£ 56,875,837	£ 251,340,686	845.75	1237.55	£ 606,516	£ 426,163
BSC	£ 182,927	£ -	£ 40,472,763	£ 40,655,689	498.38	743.17		
Analysis using all available treatments assuming discounts								
NBS screening	£ 12,690,148	£ 68,824,724	£ 23,272,399	£ 104,787,272	1432.71	1752.09	-£ 15,570	-£ 17,762
No NBS screening	£ 182,628	£ 56,868,003	£ 56,875,837	£ 113,926,468	845.75	1237.55	£ 210,930	£ 148,209
BSC	£ 182,927	£ -	£ 40,472,763	£ 40,655,689	498.38	743.17		
Analysis using zolgensma only, and at list price								
NBS screening	£ 12,690,148	£ 91,918,576	£ 30,522,146	£ 135,130,870	1390.29	1742.25	-£ 2,352	-£ 2,668
No NBS screening	£ 182,628	£ 72,714,759	£ 63,602,370	£ 136,499,757	808.18	1229.14	£ 309,367	£ 197,224
BSC	£ 182,927	£ -	£ 40,472,763	£ 40,655,689	498.38	743.17		
Analysis using zolgensma only, and at 30% discount								
NBS screening	£ 12,690,148	£ 64,396,667	£ 30,522,146	£ 107,608,961	1390.29	1742.25	-£ 12,229	-£ 13,874
No NBS screening	£ 182,628	£ 50,942,783	£ 63,602,370	£ 114,727,782	808.18	1229.14	£ 239,091	£ 152,423

BSC	£ 182,927	£ -	£ 40,472,763	£ 40,655,689	498.38	743.17		

Results of scenario analyses using lower incidence of SMA

Table 38 presents the cost-effectiveness results in the scenario where incidence was assumed to be lower i.e. 1 in 14,000 (rather than the 1 in 8200 assumed in the base case analyses). In all the analyses, NBS screening seems to be cost saving and more effective compared to No NBS screening.

Table 38. Cost-effectiveness results of scenario using lower incidence of SMA

	Screening/ Diagnosis Costs	**Treatment Costs**	**Health Care Costs**	**Total Costs**	**QALYs**	**LYs**	**Incremental Results**	
							Cost/QALY Gained	**Cost/LY Gained**
Analysis using all available treatments and list prices								
NBS screening	£ 6,603,087	£ 126,325,819	£ 13,630,977	£ 146,559,882	839.16	1026.22	-£ 1,902	-£ 2,170
No NBS screening	£ 106,968	£ 113,793,872	£ 33,312,990	£ 147,213,830	495.37	724.85	£ 606,516	£ 426,163
BSC	£ 107,143	£ -	£ 23,705,475	£ 23,812,618	291.91	435.29		
Analysis using all available treatments assuming discounts								
NBS screening	£ 6,603,087	£ 40,311,624	£ 13,630,977	£ 60,545,688	839.16	1026.22	-£ 17,984	-£ 20,515
No NBS screening	£ 106,968	£ 33,308,402	£ 33,312,990	£ 66,728,360	495.37	724.85	£ 210,930	£ 148,209
BSC	£ 107,143	£ -	£ 23,705,475	£ 23,812,618	291.91	435.29		
Analysis using zolgensma only, and at list price								
NBS screening	£ 6,603,087	£ 53,838,023	£ 17,877,257	£ 78,318,367	814.31	1020.46	-£ 4,785	-£ 5,429
No NBS screening	£ 106,968	£ 42,590,073	£ 37,252,817	£ 79,949,858	473.36	719.92	£ 309,367	£ 197,224
BSC	£ 107,143	£ -	£ 23,705,475	£ 23,812,618	291.91	435.29		
Analysis using zolgensma only, and at 30% discount								

NBS screening	£ 6,603,087	£ 37,718,048	£ 17,877,257	£ 62,198,392	814.31	1020.46	-£ 14,663	-£ 16,635
No NBS screening	£ 106,968	£ 29,837,916	£ 37,252,817	£ 67,197,701	473.36	719.92	£ 239,091	£ 152,423
BSC	£ 107,143	£ -	£ 23,705,475	£ 23,812,618	291.91	435.29		

Results of scenario analyses using 1.5% discount for health outcomes

Table 39 presents the cost-effectiveness results in the scenario where 1.5% discount rate was used for the health outcomes (i.e. LYs and QALYs). In all the analyses, NBS screening seems to be cost saving and more effective compared to No NBS screening.

Table 39. Cost-effectiveness results of scenario using 1.5% discount rate for health outcomes

	Screening/ Diagnosis Costs	**Treatment Costs**	**Health Care Costs**	**Total Costs**	**QALYs**	**LYs**	**Incremental Results**	
							Cost/QALY Gained	**Cost/LY Gained**
Analysis using all available treatments and list prices								
NBS screening	£ 6,690,148	£ 215,678,227	£ 23,272,399	£ 245,640,775	2343.71	2912.54	-£ 5,268	-£ 5,311
No NBS screening	£ 182,628	£ 194,282,221	£ 56,875,837	£ 251,340,686	1261.71	1839.24	£ 398,739	£ 280,019
BSC	£ 182,927	£ -	£ 40,472,763	£ 40,655,689	733.34	1086.84		
Analysis using all available treatments assuming discounts								
NBS screening	£ 6,690,148	£ 68,824,724	£ 23,272,399	£ 98,787,272	2343.71	2912.54	-£ 13,992	-£ 14,105
No NBS screening	£ 182,628	£ 56,868,003	£ 56,875,837	£ 113,926,468	1261.71	1839.24	£ 138,671	£ 97,383
BSC	£ 182,927	£ -	£ 40,472,763	£ 40,655,689	733.34	1086.84		
Analysis using zolgensma only, and at list price								
NBS screening	£ 6,690,148	£ 91,918,576	£ 30,522,146	£ 129,130,870	2256.23	2873.95	-£ 6,832	-£ 6,813
No NBS screening	£ 182,628	£ 72,714,759	£ 63,602,370	£ 136,499,757	1177.68	1792.33	£ 215,697	£ 135,854

BSC	£ 182,927	£ -	£ 40,472,763	£ 40,655,689	733.34	1086.84		
Analysis using zolgensma only, and at 30% discount								
NBS screening	£ 6,690,148	£ 64,396,667	£ 30,522,146	£ 101,608,961	2256.23	2873.95	-£ 12,163	-£ 12,129
No NBS screening	£ 182,628	£ 50,942,783	£ 63,602,370	£ 114,727,782	1177.68	1792.33	£ 166,699	£ 104,994
BSC	£ 182,927	£ -	£ 40,472,763	£ 40,655,689	733.34	1086.84		

Scenario analysing impact of earlier diagnosis and treatment

In the base case analyses, it was assumed that the average time taken for diagnosis and treatment is around 3 weeks, and by this time 52% of the patients with 2 SMN2 copies would show symptoms and would receive early symptomatic treatment.

Clinical experts suggested that around 1-2% of new patients with 2 SMN2 copies would show symptoms each day, and this was used to perform scenario analyses with shorter diagnostic time interval of NBS (e.g. 2 weeks compared to the base case of 3 weeks), where more patients with 2 SMN2 copies would receive presymptomatic treatment. Given the uncertainty in estimating the costs associated with amending the screening pathway for earlier diagnosis, this scenario analysis focuses only on the health benefits.

A scenario was performed, using all available treatments, where it was assumed that 75% of patients would be treated presymptomatically and the rest would receive early symptomatic treatment, which resulted in an additional 77.5 discounted QALYs compared to the base case analyses.

In another scenario using zolgensma only, where it was assumed that 75% of patients would be treated presymptomatically and the rest would receive early symptomatic treatment, which resulted in an additional 76.54 discounted QALYs compared to the base case analyses.

Results of probabilistic sensitivity analysis

The results presented in the following section include the effects of accounting for uncertainty in the model parameters (the costs, utilities, and other parameters), characterised as probability distributions. Probabilistic sensitivity analysis (PSA) is undertaken whereby the model is rerun (1000 times), each time with a different value for the parameters, which are sampled from the probability distributions.

The scatterplot of the cost-effectiveness plane shows the incremental costs (y-axis) and incremental QALYs (x-axis) for each of the PSA runs. In this chart, if a model run for NBS screening had exactly the same costs and QALYs as No NBS screening then the ‘sample’ for

that model run would appear at the origin. Samples plotted to the right of the y-axis have more QALYs than No NBS screening and samples plotted above the x-axis have more costs.

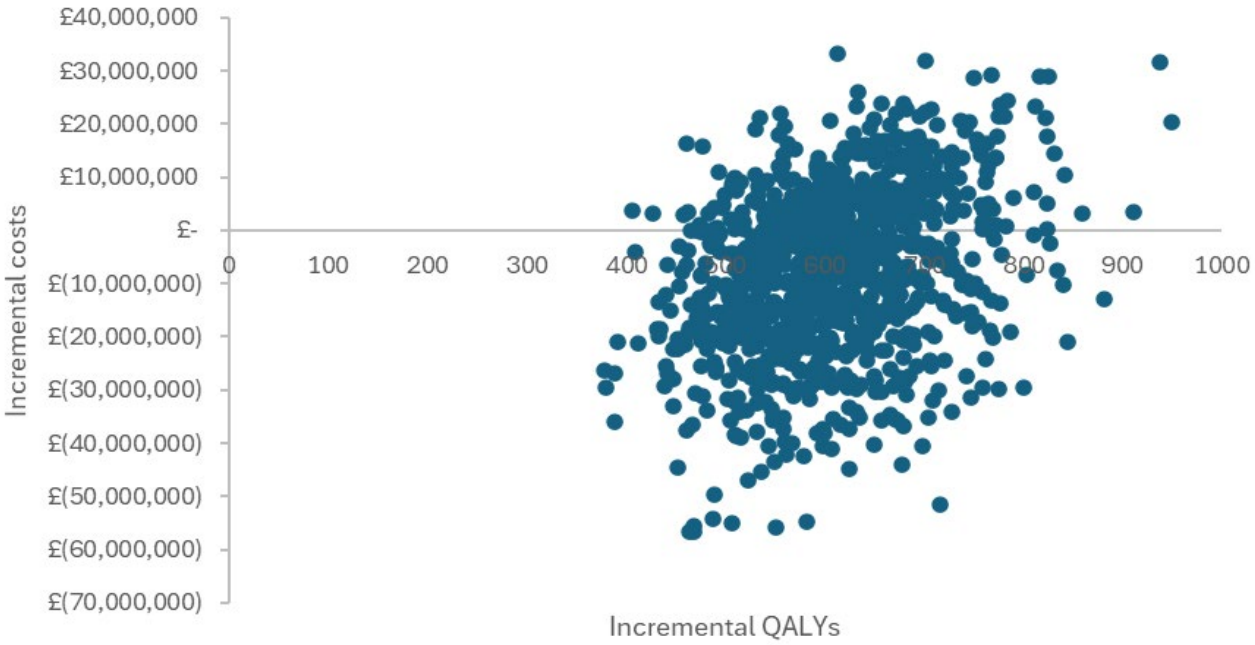
The cost-effectiveness acceptability curve (CEAC) shows the proportion of model runs for which each strategy is cost-effective over a range of potential willingness-to-pay thresholds.

Probabilistic results of base case analysis using all available treatments and list prices

Figure 7 presents the scatterplot of the cost-effectiveness plane, which shows the incremental costs (y-axis) and incremental QALYs (x-axis) for each of the PSA runs.

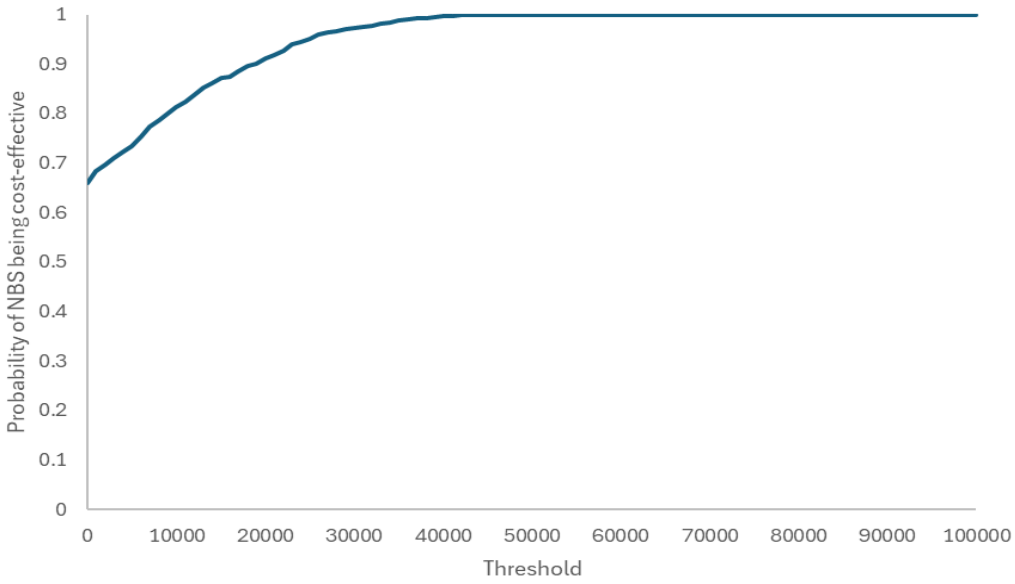
As the model is rerun 1000 times, each time with a different value for the parameters sampled from the probability distribution, in some of the sampled model runs NBS screening is more costly than No NBS screening. Also, whilst there is uncertainty in the magnitude of incremental QALYs, NBS screening is always more effective than No NBS screening (i.e. NBS screening always has higher QALYs compared to No NBS screening).

Figure 7. Scatterplot of incremental costs and QALYs of NBS compared to No NBS (analysis using all avail-able treatments and list prices)



The cost-effectiveness acceptability curve (CEAC) in Figure 8 shows the proportion of model runs for which NBS screeening is cost-effective over a range of potential willingness-to-pay thresholds. At a threshold of £20,000/QALY, the percentage of model runs in which NBS screening was the most cost-effective strategy was around 90%, suggesting a 90% probability of NBS being cost-effective.

Figure 8. Probability of NBS being cost-effective at different thresholds (analysis using all available treatments and list prices)



Probabilistic results of base case analysis using all available treatments and price discounts

In this analysis using price discounts, almost all of the sampled model runs in Figure 9 are below x-axis suggesting that NBS screening is less costly and more effective than No NBS screening. This can also be observed in Figure 10 which suggests 100% probability of NBS screening being cost-effective at thresholds greater than £20,000/QALY.

Figure 9. Scatterplot of incremental costs and QALYs of NBS compared to No NBS (analysis using all available treatments and price discounts)

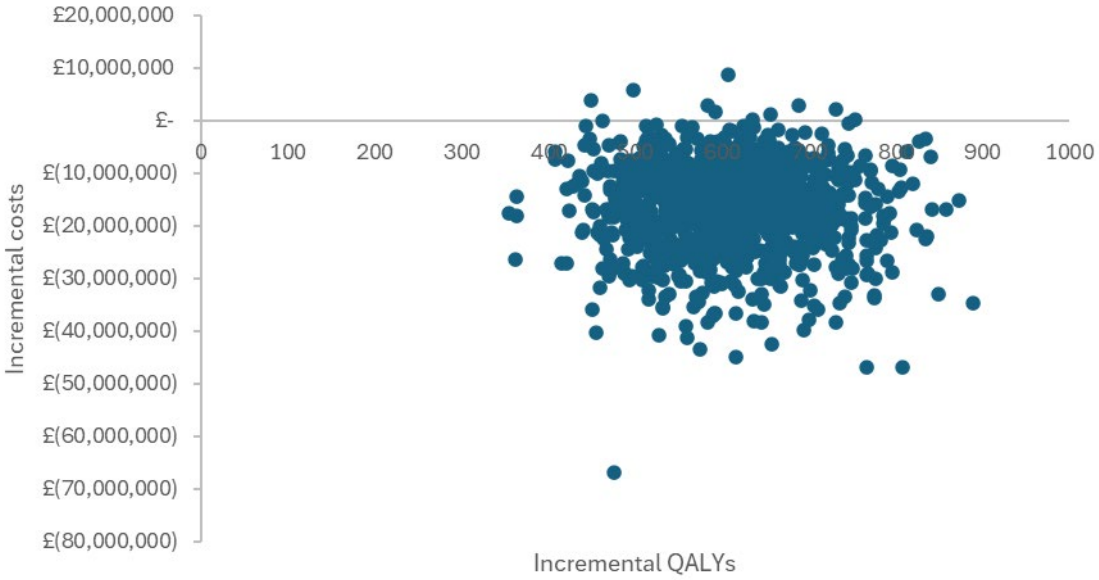
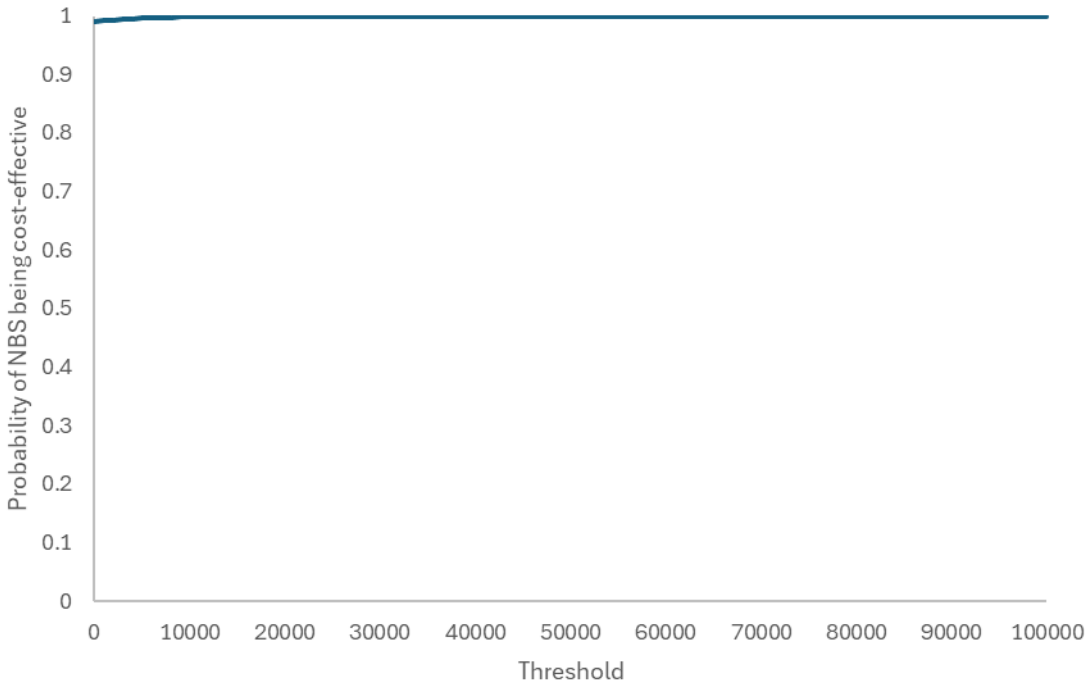


Figure 10. Probability of NBS being cost-effective at different thresholds (analysis using all available treatments and with price discounts)



Probabilistic results of base case analysis using zolgensma only and list prices

In the scatterplot presented in Figure 11, NBS screening always has higher QALYs compared to No NBS screening, but it is also more costly in some of the sampled model runs. This is also reflected in Figure 12 which suggests NBS screening has 99% probability of being cost-effective at a threshold of £20,000/QALY.

Figure 11. Scatterplot of incremental costs and QALYs of NBS compared to No NBS (analysis using zolgensma only and list prices)

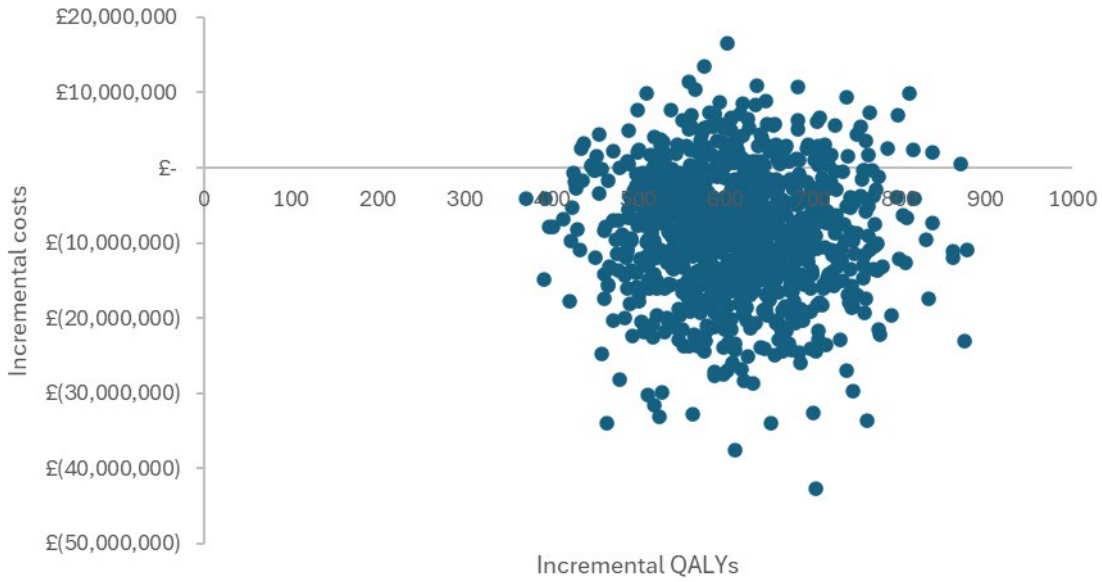
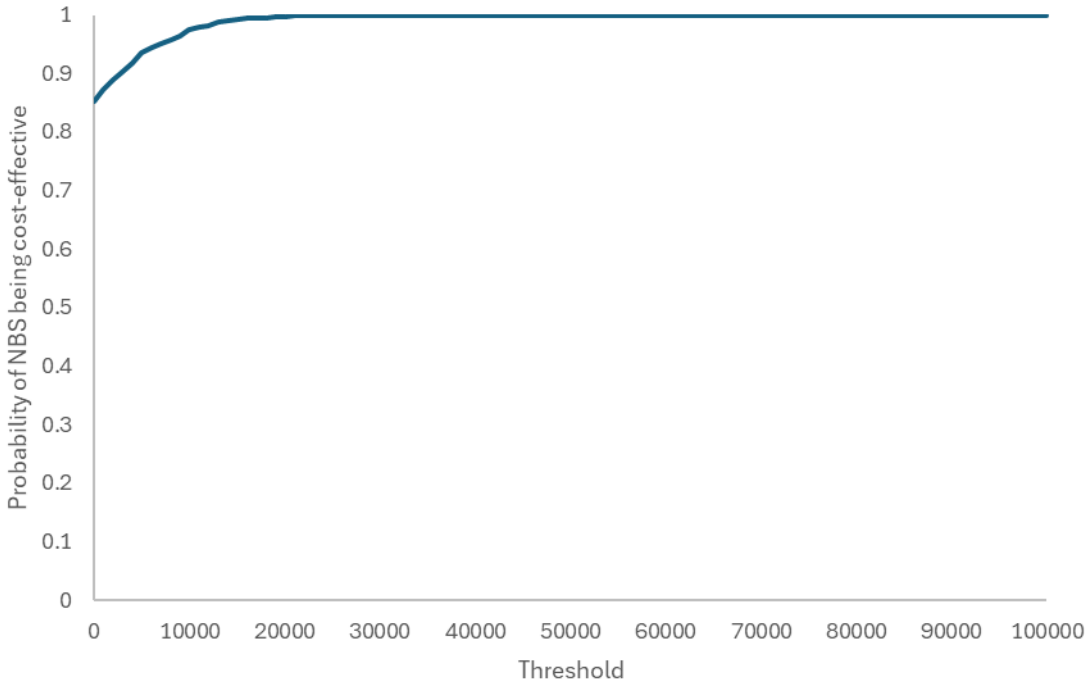


Figure 12. Probability of NBS being cost-effective at different thresholds (analysis using zolgensma only and list prices)



Probabilistic results of base case analysis using zolgensma only and 30% discount

In this analysis using price discounts, almost all of the sampled model runs in Figure 13 are below x-axis suggesting that NBS screening is less costly and more effective than No NBS screening. This can also be observed in Figure 14 which suggests 100% probability of NBS screening being cost-effective at thresholds greater than £20,000/QALY.

Figure 13. Scatterplot of incremental costs and QALYs of NBS compared to No NBS (analysis using zolgensma only and 30% discount)

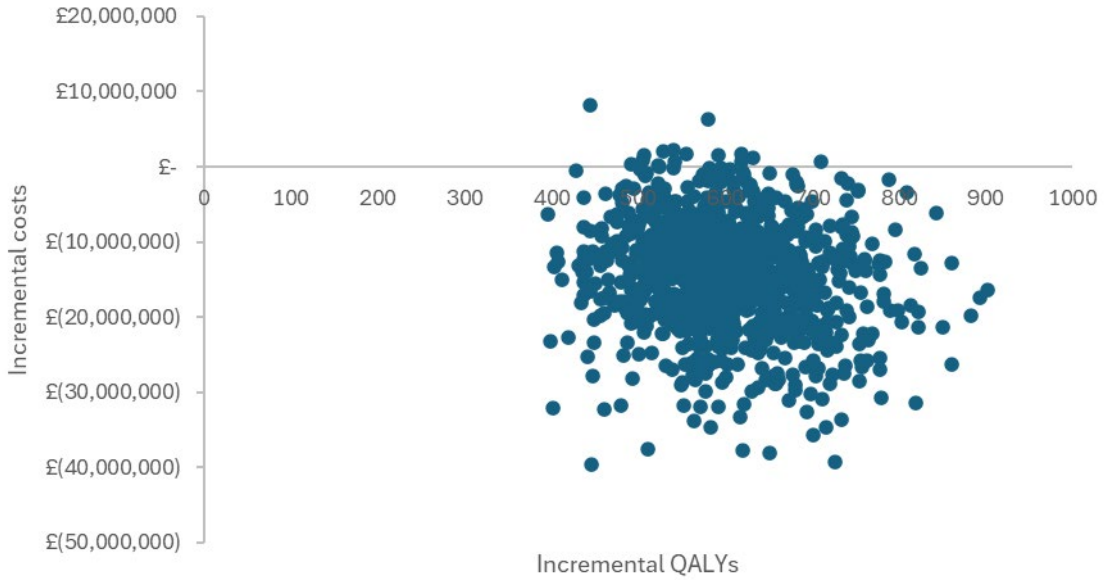
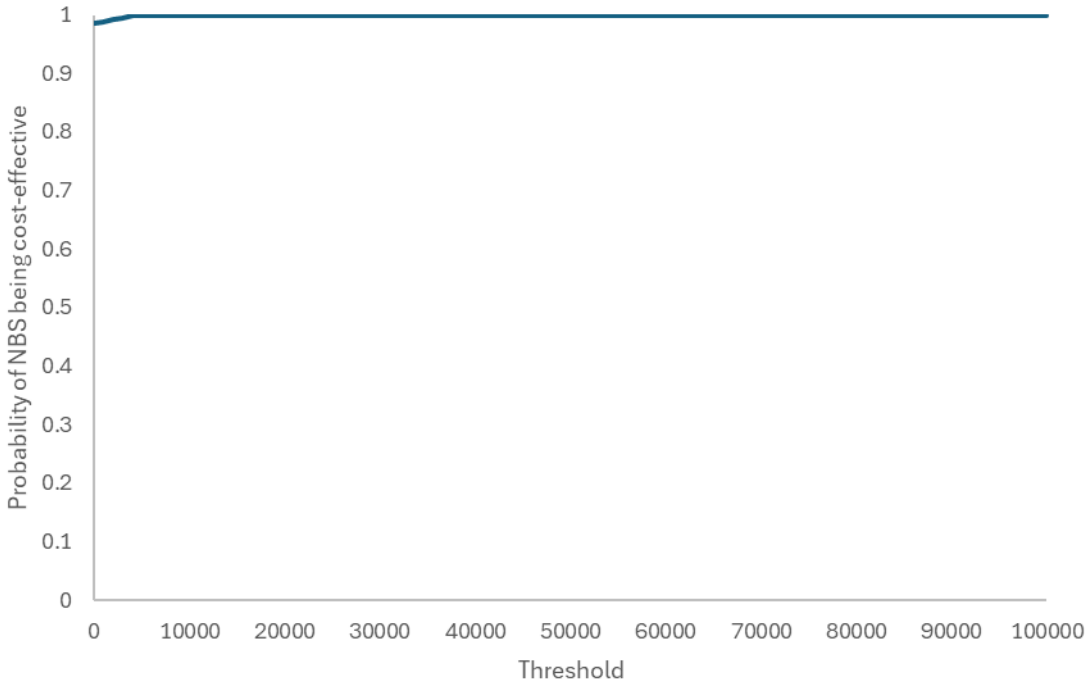


Figure 14. Probability of NBS being cost-effective at different thresholds (analysis using zolgensma only and 30% discount)



Discussion

Overview

A *de novo* model was developed to estimate the cost-effectiveness of NBS for SMA, informed by key clinical trials and relevant published literature.

Costs and benefits of newborn blood spot screening

NBS screening allows detection of most of the cases (n=69.44) of SMA presymptomatically with the rest of 3.73 cases detected symptomatically (i.e. the 5% of patients who do not have homozygous deletions in SMN1) while in No NBS screening arm of the model, 0.73 cases of SMA were detected presymptomatically via family history with the rest of 72.44 cases detected symptomatically. This allows more patients in NBS screening arm to receive presymptomatic treatment which is more effective than symptomatic treatment.

Based on current clinical data (and assuming all 3 drugs are available), by the end of the 3 years, compared with current practice of No NBS screening, NBS would prevent 2 cases requiring permanent ventilation, around 3 early deaths, and about 30 cases being confined to a sitting state. NBS screening also enables about 37 more cases to live a broadly normal life. However, NBS screening will identify around 3 cases with 5 SMN2 copies, those who will not be affected until adulthood if at all, and this may be detrimental to their health and wellbeing.

Also, an additional cost of £6.7 million is required to operationalise NBS each year which is offset by the long-term cost savings due to lower health care costs (see below).

3-year and long-term outcomes

In the No NBS screening arm, where patients are detected symptomatically and receive pharmacological treatment, the number of deaths and patients on PV are low but most of the patients are in the sitting health state with only a few patients achieving walking with assistance or BRND. In the NBS screening arm, where most patients receive pharmacological treatment presymptomatically, most of the patients achieve BRND with the number of deaths and patients on PV and patients in sitting health state further reduced.

In the No NBS screening arm, where most of the patients are in the sitting health state, the lower survival of patients in sitting health states is reflected in their long-term outcomes . The survival in the NBS screening arm is much higher than that in the No NBS screening arm due to lower short-term deaths, fewer patients in PV, and fewer patients in sitting health states. Also, most of the patients in the NBS screening arm are in the BRND state (which has survival of general population) and this is reflected in better long-term outcomes of patients in NBS screening arm.

Cost-effectiveness results

Given the uncertainty in the reimbursement status of the treatments in the future and the lack of "actual" prices, the base case analyses included 4 different analyses. All the analyses suggested that NBS screening dominates No NBS screening i.e. NBS screening has higher QALYs and lower costs compared to No NBS screening. The cost savings depended on the treatment mix used and the price of treatments (i.e. whether list price was used or whether discounts were applied).

However, NBS screening is not cost-effective when compared to BSC in the analysis using all available treatments and list prices. In the other 3 analyses (i.e. using all available treatments assuming discounts, using zolgensma only and at list price, and using zolgensma only with price discounts), NBS screening is cost-effective when compared to BSC at thresholds of £100,000/QALY used for NICE highly specialised technologies (HSTs). However, when typical NICE thresholds of £20,000/QALY to £30,000/QALY are used, NBS screening is not cost-effective when compared to BSC.

Key uncertainties and limitations

Table 40 below outlines the key uncertainties and limitations of the model. NICE is currently appraising nusinersen and risdiplam for symptomatic and presymptomatic treatment of SMA, with the recommendations scheduled for November 2025. As such, there is substantial uncertainty in the reimbursement status of the treatments in the future. To address this issue, the base case analyses assumed all treatments would be available according their current eligibility as reported in Table 1, and a scenario analysis was performed assuming only Zolgensma is available (i.e. if nusinersen and risdiplam were not approved).

It should also be noted that the costs of treatments are under confidential patient access schemes in the NHS, and as such, the "actual" prices of these treatments are unknown. Without access to this confidential pricing data, the list prices for the treatment costs were used in the base case analyses. However, analyses were performed using discounts to understand the impact on cost-effectiveness.

There is also uncertainty in the effectiveness of presymptomatic and symptomatic treatment, with limited longer-term data. In particular, there is uncertainty in terms of the impact of diagnostic delay on the number of patients becoming symptomatic with Type 1 SMA, and subsequently the impact on outcomes achieved. Also, most of the cost savings of NBS screening are by avoiding the costs in the sitting health state. As such, if the costs in the sitting health state are lower than those used in the model, NBS screening could be less cost-effective.

Table 40. Key uncertainties and limitations

Limitation	Potential impact	Potential impact on findings
Price of treatments unknown	See scenario analyses Depends on type of treatment(s) in NBS and No NBS (as Risdiplam & Nusinersen are for lifetime)	
Reimbursement status unknown		
Effectiveness of symptomatic treatment unknown	Better effectiveness of symptomatic treatment means lower incremental benefits of screening	NBS less cost-effective/cost-saving
Long-term effectiveness/ treatment waning unknown	If there is treatment waning, outcomes will be lower in screening arm	NBS likely less cost-effective/cost-saving
Incidence of SMA uncertain	Lower incidence results in lower incremental benefits	NBS less cost-effective/cost-saving
Costs of “sitting” health state uncertain	Lower costs result in lower cost savings	NBS less cost-effective/cost-saving

Conclusions and Further work

The analyses from the *de novo* model suggest that NBS screening is cost-effective compared to current practice of No NBS screening and symptomatic treatment, but may not be cost-effective when compared to the hypothetical BSC arm. The cost-effectiveness of NBS screening is dependent on the reimbursement status (uncertain till at least November 2025) and the actual prices of the treatments (which are under confidential discounts).

The *de novo* model was populated using best available data from the published literature, however, there is an SMA In Service Evaluation (ISE) planned which will capture data specific to the UK. As such, the model can include the data from the ISE to provide an updated estimate of cost-effectiveness of NBS screening in the UK.

References

1. Weidlich D, Bischof M, O'Rourke D. Cost Effectiveness of Heel-Prick Screening Test for Spinal Muscular Atrophy (SMA) in Ireland. Developmental Medicine and Child Neurology. 2023 Jan;65(Supplement 1):91.

2. Thiem H. Cost-effectiveness analysis - Cost-effectiveness of newborn screening for spinal muscular atrophy. [German]. Gesundheitsokonomie und Qualitatsmanagement. 2022 Dec 16;27(6):282.

3. 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 Journal of Rare Diseases Conference: 10th European Conference on Rare Diseases and Orphan Products, ECRD. 2020;15(SUPPL).

4. Weidlich D, Servais L, Kausar I, Howells R, Bischof M. Cost-Effectiveness of Newborn Screening for Spinal Muscular Atrophy in England. Neurology & Therapy. 2023;12(4):1205–20.

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. Journal of Pediatrics. 2020;227:274-280.e2.

6. Dangouloff T, Thokala P, Stevenson MD, Deconinck N, D'Amico A, Daron A, et al. Cost-effectiveness of spinal muscular atrophy newborn screening based on real-world data in Belgium. Neuromuscular Disorders. 2024 Jan;34:61–7.

7. Shih ST, Farrar MA, Wiley V, Chambers G. Newborn screening for spinal muscular atrophy with disease-modifying therapies: a cost-effectiveness analysis. Journal of Neurology, Neurosurgery & Psychiatry. 2021;92(12):1296–304.

8. Landfeldt E. The cost-effectiveness of newborn screening for spinal muscular atrophy. Developmental Medicine & Child Neurology. 2022 Jun 14;14:14.

9. 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 in Health. 2022;25(10):1696–704.

10. Dangouloff T, Botty C, Beaudart C, Servais L, Hiligsmann M. Systematic literature review of the economic burden of spinal muscular atrophy and economic evaluations of treatments. Orphanet Journal Of Rare Diseases. 01 23;16(1):47.

11. Muller-Felber W, Blaschek A, Schwartz O, Glaser D, Nennstiel U, Brockow I, et al. Newbornscreening SMA - From Pilot Project to Nationwide Screening in Germany. Journal of neuromuscular diseases. 2023;10(1):55–65.

12. Vill K, Schwartz O, Blaschek A, Glaser D, Nennstiel U, Wirth B, et al. Newborn screening for spinal muscular atrophy in Germany: clinical results after 2 years. Orphanet Journal Of Rare Diseases. 2021;16(1):153.

13. Boemer F, Caberg JH, Beckers P, Dideberg V, di Fiore S, Bours V, et al. Three years pilot of spinal muscular atrophy newborn screening turned into official program in Southern Belgium. Scientific Reports. 2021;11(1):19922.

14. Wallace S, Orstavik K, Rowe A, Strand J. National newborn screening for SMA in Norway. Neuromuscular Disorders. 2023 Oct;33(Supplement 1):S90.

15. Belter L, O'Brien S, Jarecki J. Self-reported SMN2 Copy Number and Current Motor Function from the Cure SMA Patient Database. Neurology Conference: 73rd Annual Meeting of the American Academy of Neurology, AAN [Internet]. 2021;96(15 SUPPL 1). Available from: https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed22&AN=635947797

16. Calucho M, Bernal S, Alias L, March F, Vencesla A, Rodriguez-Alvarez FJ, et al. Correlation between SMA type and SMN2 copy number revisited: An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. Neuromuscular Disorders. 3AD;28(3):208–15.

17. Kekou K, Svingou M, Sofocleous C, Mourtzi N, Nitsa E, Konstantinidis G, et al. Evaluation of Genotypes and Epidemiology of Spinal Muscular Atrophy in Greece: A Nationwide Study Spanning 24 Years. Journal of neuromuscular diseases. 2020;7(3):247–56.

18. Konig K, Pechmann A, Thiele S, Walter MC, Schorling D, Tassoni A, et al. De-duplicating patient records from three independent data sources reveals the incidence of rare neuromuscular disorders in Germany. Orphanet Journal Of Rare Diseases. 06 24;14(1):152.

19. Ogino S, Wilson RB. Spinal muscular atrophy: molecular genetics and diagnostics. Expert Review of Molecular Diagnostics. 2004 Jan 1;4(1):15–29.

20. Strauss K, Muntoni F, Farrar M, Saito K, Mendell J, Servais L, et al. Onasemnogene Abeparvovec for Presymptomatic Infants with Spinal Muscular Atrophy and Two Copies of SMN2. Neurology Conference: 74th Annual Meeting of the American Academy of Neurology, AAN [Internet]. 2022;98(18 SUPPL). Available from: https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emexb&AN=638416728

21. Servais L, Finkel R, Farrar M, Vlodavets D, Zanoteli E, Al-Muhaizea M, et al. 21O RAINBOWFISH: 2-year efficacy and safety data of risdiplam in infants with presymptomatic SMA. Neuromuscular Disorders. 2024 Oct 1;43:104441.738.

22. Crawford TO, Swoboda KJ, De Vivo DC, Bertini E, Hwu WL, Finkel RS, et al. Continued benefit of nusinersen initiated in the presymptomatic stage of spinal muscular atrophy: 5-year update of the NURTURE study. Muscle and Nerve. 2023 Aug;68(2):157–70.

23. Masson R, Boespflug-Tanguy O, Darras BT, Day JW, Deconinck N, Klein A, et al. FIREFISH parts 1 and 2: 24-month safety and efficacy of risdiplam in type 1 SMA. European Journal of Neurology. 2021 Jun;28(SUPPL 1):395–6.

24. Deconinck N, Baranello G, Boespflug-Tanguy O, Day J, Klein A, Masson R, et al. FIREFISH Parts 1 and 2: 36-month safety and efficacy of risdiplam in Type 1 spinal muscular atrophy. European Journal of Neurology. 2022 Jul;29(Supplement 1):279.

25. Castro D, Finkel RS, Farrar MA, Tulinius M, Krosschell KJ, Saito K, et al. Nusinersen in infantile-onset spinal muscular atrophy: Results from longer-term treatment from the open-label shine extension study. Neurology Conference: 72nd Annual Meeting of the American Academy of Neurology, AAN [Internet]. 2020;94(15 Supplement). Available from: https://ovidsp.ovid.com/ovid-web.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed21&AN=633068864

26. Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. New England Journal of Medicine. 2018;378(7):625–35.

27. Darras BT, Farrar MA, Mercuri E, Finkel RS, Foster R, Hughes SG, et al. An Integrated Safety Analysis of Infants and Children with Symptomatic Spinal Muscular Atrophy (SMA) Treated with Nusinersen in Seven Clinical Trials. CNS Drugs. 9AD;33(9):919–32.

28. Gregoretti C, Ottonello G, Chiarini Testa MB, Mastella C, Ravà L, Bignamini E, et al. Survival of Patients With Spinal Muscular Atrophy Type 1. Pediatrics. 2013 May 1;131(5):e1509–14.

29. Zerres K, Wirth B, Rudnik-Schoneborn S. Spinal muscular atrophy - Clinical and genetic correlations. Neuromuscular Disorders. 1997 May;7(3):202–7.

30. Lopez-Bastida J, Pena-Longobardo LM, Aranda-Reneo I, Tizzano E, Sefton M, Oliva-Moreno J. Social/economic costs and health-related quality of life in patients with spinal muscular atrophy (SMA) in Spain. Orphanet Journal Of Rare Diseases. 08 18;12(1):141.

31. Tappenden P, Hamilton J, Kaltenthaler E, Hock E, Rawdin A, Mukuria C. Nusinersen for treating spinal muscular atrophy: a single technology appraisal. School of Health and Related Research (ScHARR); 2018.

32. Landfeldt E, Edstrom J, Sejersen T, Tulinius M, Lochmuller H, Kirschner J. Quality of life of patients with spinal muscular atrophy: A systematic review. European Journal of Paediatric Neurology. 2019 May;23(3):347–56.

33. Carter M, Tobin A, Coy L, McDonald D, Hennessy M, O'Rourke D. Room to improve: The diagnostic journey of Spinal Muscular Atrophy. European Journal of Paediatric Neurology. 2023;42:42–6.

34. Maggi L, Vita G, Marconi E, Taddeo D, Davi M, Lovato V, et al. Opportunities for an early recognition of spinal muscular atrophy in primary care: a nationwide, population-based, study in Italy. Family Practice. 2022 Aug 11;11:11.

35. Wiedmann L, Cairns J. Review of economic modeling evidence from NICE appraisals of rare disease treatments for spinal muscular atrophy. Expert Review of Pharmacoeconomics & Outcomes Research. 2023 Jun;23(5):469–82.

Appendix 1 - Treatment effectiveness data and model assumptions

In order to populate the model, assumptions had to be made to account for both normal milestone development and the limited published data from the pivotal trials. The key assumptions for each population are outlined below. Until patients show symptoms, they are assumed to be in the broad range of normal development (BRND) health state.

Accounting for normal milestone development in the model

Each model health state i.e. Permanent Ventilation (PV), Not Sitting, Sitting, Walking with assistance, Broad Range of Normal Development (BRND) has a cost and a utility value associated with it to account for the impact of SMA symptoms on the patient. As the model starts from birth, no babies will be sitting or walking with assistance at the beginning. However, these babies should not incur the costs and lower utility value associated with the Not Sitting health state as it is part of normal development that they would be not sitting at this age.

In order to account for this, the normal developmental rules as shown in Figure 3 were used to adjust the milestones reported in the pivotal trials (See Tables A1 - A4). 6 months (one model cycle) was allowed over the normal WHO developmental window to account for delays between a child achieving a milestone and their next trial assessment. Some additional assumptions based on the SMA Type or number of SMN2 copy numbers were also used. A detailed description of how these assumptions relate to each set of treatment effectiveness parameters is outlined below.

Presymptomatic treatment effectiveness

Presymptomatic 2 SMN2 copies - See Table A1

Zolgesma

- 71% of patients achieved walking without assistance and therefore start the model in the BRND health state as they achieved their developmental milestones.
- 14.3% of patients achieved walking with assistance. These patients start the model in the BRND health state. However, at 24 months when they would be expected to walk without assistance, they move to the Walking with Assistance health state to reflect that the additional support they will now require.
- 14.3% of patients achieved the highest milestone of Sitting. An assumption is made that the delay to their development is known at 6 months. Therefore, these patients start the model in the Sitting health state to reflect the costs of support and the health utility impact of this.

Nusinersen & Risdiplam

- The data from Nusinersen's trial NURTURE is used for both Nusinersen and Risdiplam as RAINBOWFISH had a shorter follow up (24 months vs 36 months), did not report walking with assistance, and had a smaller trial population (5 patients vs 15 patients). Both studies reported 60% of patients walking without assistance at 24 months.

- 40% of patients were still in the sitting health state at 18months. An assumption is made that the delay to their development is known at 6 months. Therefore, these patients start the model in the Sitting health state to reflect the costs of support and the health utility impact of this.

- The other 60% of patients start the model in the BRND health state as they go on to achieve either walking with assistance by 18 months or walking alone by 24 months.

- Patients in the Sitting health state continue to improve but with a delay to their development which is reflected in the health state costs to reflet the support they would need to receive.

Table A1: Presymptomatic 2 SMN2 copies

Zolgensma – based on SPRINT trial reported in Strauss et al 2022b (supplementary material) Number of patients: 14				
Month	**Not sitting**	**Sitting**	**Walking with assis-tance**	**Broad range of normal development**
6	0%	14.30%	0%	85.70%
12	0%	14.30%	0%	85.70%
18	0%	14.30%	0%	85.70%
24	0%	14.30%	14.30%	71.40%
30	0%	14.30%	14.30%	71.40%
36	0%	14.30%	14.30%	71.40%
Nusinersen & Risdiplam* – based on NURTURE trial reported in Crawford et al 2023 Number of patients: 15				
Month	**Not sitting**	**Sitting**	**Walking with assis-tance**	**Broad range of normal development**
6	0%	40.00%	0%	60%
12	0%	40.00%	0%	60%
18	0%	40%	0%	60%

24	0%	20%	20%	60%
30	0%	20%	0%	80%
36	0%	13.30%	0%	86.70%

- Due to low number in the Risdiplam trial (see Table A1), equivalent effectiveness was assumed between Nusinersen and Risdiplam

Early symptomatic 2 SMN2 copies (screened but symptomatic prior to treatment) – see Table A2

- Based on Aragon-Gawinska study where 76% of those with 2 SMN2 copies achieved ambulation when treated asymptomatically compared to 19% of those treated who were early symptomatic, we have assumed that the proportion of patients in the walking or BRND health states would be 25% of those treated presymptomatically.

- The proportion of patients in the non-sitting health state is taken as the average between the symptomatic and presymptomatic for each treatment with the remainder of patients in the sitting health state.

- Outcomes are better than the symptomatically treated Type 1 patients with no patients dying or entering the permanent ventilation health state within the first 3 years.

Table A2: Early symptomatic 2 SMN2 copies

Zolgensma				
Month	**Not sitting**	**Sitting**	**Walking with assistance**	**Broad range of normal development**
6	22.70%	55.88%		21.43%
12	22.70%	55.88%		21.43%
18	22.70%	55.88%	3.58%	17.85%
24	13.15%	65.43%	3.58%	17.85%
30	13.15%	65.43%	3.58%	17.85%
36	8.35%	70.23%	3.58%	17.85%
Nusinersen & Risdiplam*				
Month	**Not sitting**	**Sitting**	**Walking with assistance**	**Broad range of normal development**
6	34.74%	50.27%		15.00%
12	34.74%	50.27%		15.00%
18	34.74%	50.27%	3.33%	11.67%
24	28.03%	51.98%	5.00%	15.00%

30	20.79%	59.22%	0.00%	20.00%
36	13.55%	64.78%	0.00%	21.68%

- Due to low number in the Risdiplam trial (see Table A1) equivalent effectiveness was assumed between Nusinersen and Risdiplam

Presymptomatic 3 SMN2 copies - See Table A3

Zolgensma

- 93% of patients achieved walking without assistance by 24 months and therefore start the model in the BRND as they achieved their developmental milestone.
- 7% of patients of patients had only achieved the ability to sit at 18 months and therefore start the model in the Sitting health state. They had not achieved the ability to walk at the end of the reported follow up (24 months). An assumption is made that the delay to their development is known at 6 months and the patients start in the Sitting health state to reflect the costs of support and the health utility impacts of this.

Risdiplam

- While 8% of patients are only sitting at 18 months this may reflect that RAINBOWFISH did not report walking with assistance. All patients are walking without assistance at 24 months. Therefore, it is assumed that all patients start and remain in the BRND health state.

Nusinersen

- All patients achieve walking without assistance by age 18 months. Therefore, it is assumed that all patients start and remain in the BRND health state.

Table A3: Presymptomatic 3 SMN2 copies

Zolgensma – based on SPRINT trial reported in Strauss et al 2022b (supplementary material) **Number of patients N: 15**				
Month	**Not sitting**	**Sitting**	**Walking with assistance**	**BRND**
6		6.7%		93.3%
12		6.7%		93.3%
18		6.7%		93.3%
24		6.7%		93.3%
30		6.7%		93.3%
36		6.7%		93.3%
Risdiplam – based on RAINBOWFISH trial (Farrar et al 2024 - conference poster); N = 13				

Month	Not sitting	Sitting	Walking with assistance	BRND
6		0%	N/R	100%
12		0%	N/R	100%
18		0%	N/R	100%
24		0%	N/R	100%
30		0%	N/R	100%
36		0%	N/R	100%
Nusinersen – based on NURTURE trial reported in Crawford et al 2023; Number of patients: 10				
Month	**Not sitting**	**Sitting**	**Walking with assistance**	**BRND**
6		0%		100%
12		0%		100%
18		0%		100%
24		0%		100%
30		0%		100%
36		0%		100%

Presymptomatic 4 SMN2 copies

As there is no data for the effectiveness of presymptomatic treatment for patients with 4 SMN2 copies, it was assumed to be 100% for all motor function milestones (i.e. the same as general population).

Symptomatic treatment effectiveness

Symptomatic Type 1 SMA - see Table A4

Zolgesma

- As 51% of patients achieve the ability to sit by 18 months it is assumed that 51% of patients start the model in the Sitting health state. This reduces the proportion of patients in the Not Sitting health state in months 6 and 12 compared to the trial data.

- From month 18 onwards the health state proportions are directly taken from the trial data.

Nusinersen and Risdiplam

- The same treatment effectiveness is assumed for Nusinersen and Risdiplam with data from Risdiplam's trial FIREFISH used. In their respective trials Nusinersen has substantially more patients in the permanent ventilation health state than the trials for both Risdiplam and Zolgensma. This indicates differences in the trial populations rather than differences in treatment effectiveness.

- As FIREFISH only reported every 12 months the average between the two years was used to estimate the 6, 18, and 30 month proportions.

- As it was estimated that 30.53% of patients achieved the ability to sit by 18 months, it is assumed that 31% of patients start the model in the Sitting health state. This reduces the proportion of patients in the Not Sitting health state in months 6 and 12 compared to the trial data.

- From month 18 onwards the health state proportions are directly taken from the trial data.

Table A4: Symptomatic Type 1

Zolgensma – pooled StriveEU & StriveUS (post 18 month based on improvement seen in START extension) Number of patients 55 (StriveEU & Strive US) 10 (START)						
Month	**Perma-nent Ven-tilation**	**Not sit-ting**	**Sitting**	**Walking with as-sistance**	**Broad range of normal de-velopment**	**Dead**
6		47.30%	50.90%			1.80%

12	3.60%	40.00%	50.90%	1.90%		3.60%
18	3.60%	38.20%	50.90%		3.70%	3.60%
24	3.60%	19.10%	70%		3.70%	3.60%
30	3.60%	19.10%	70%		3.70%	3.60%
36	3.60%	9.50%	79.60%		3.70%	3.60%
Risdiplam & Nusinersen – based on FIREFISH trial reported in Masson et al 2022 and Deconinick et al 2022 (conference poster)* Number of patients: 41 (Masson et al 2022), 48 (Deconinick et al 2022)						
Month	**Permanent Ventilation**	**Not sitting**	**Sitting**	**Walking with assistance**	**Broad range of normal development**	**Dead**
6	0.00%	65.82%	30.53%	0.00%	0.00%	3.65%
12	0.00%	62.17%	30.53%	0.00%	0.00%	7.30%
18	1.20%	60.97%	30.53%	0.00%	0.00%	7.30%
24	2.40%	46.35%	43.95%	0.00%	0.00%	7.30%
30	6.20%	27.23%	55.30%	3.13%	0.00%	8.15%
36	10.00%	8.10%	66.65%	6.25%	0.00%	9.00%

Symptomatic Type 2 SMA - See Table A5

- The same treatment effectiveness is assumed for both Ridiplam and Nusinersen based on the Nusinersen trials. The Risdiplam trials did not report outcomes by motor milestones. Zolgesma is not approved in this population.

- 100% of patients start the model in the BRND health state as it is assumed that symptoms do not start until 12 months of age.

- At 12 months of age some patients who have gained the ability to walk with assistance start to lose this milestone. Patients begin treatment.

- With treatment some patients regain or maintain their ability to walk with assistance with 5% going on to walk without assistance at 36 months.

Table A5: Symptomatic Type 2 & 3

Nusinersen & Risdiplam for patients with Type 2 SMA – based on ENDEAR reported in Mercuri et al 2018 with longer follow up estimated from Darras et al 2019 Number of patients: 84				
Month	**Not sitting**	**Sitting**	**Walking with assistance**	**Broad range of normal develop-ment**
6		0%		100.00%
12		76.20%	23.80%	
18		91.70%	8.30%	
24		91.70%	8.30%	
30		90.50%	9.50%	
36		85.70%	9.50%	4.80%
Nusinersen & Risdiplam for patients with Type 3 SMA – based on Darras et al 2019 Number of patients: 17				
Month	**Not sitting**	**Sitting**	**Walking with assistance**	**Walking w/o as-sistance**
6				100.00%
12				100%
18				100%
24				100%
30		11.80%	11.80%	76.40%

36			11.80%	88.20%

Symptomatic Type 3 SMA - See Table A5

- The same treatment effectiveness is assumed for both Ridiplam and Nusinersen based on the Nusinersen trials. The Risdiplam trials did not report outcomes by motor milestones. Zolgesma is not approved in this population.
- 100% of patients start the model in the BRND health state as it is assumed they will be symptom free at 6 months.
- At 30 months patients become symptomatic and around 12% of patients lose the ability to walk without assistance and 12% of patients lose the ability to walk.
- With treatment patients improve and patients regain one health state.

Best supportive care – see Table A6

- Type 1 – no adjustments are made. Assume symptoms begin prior to 6 months of age
- Type 2 – all patients start in the BRND health state. Assume patients develop symptoms by 12 months of age and move to the sitting health state.
- Type 3 – all patients are in the BRND health state up to 24 months. At 30 months all patients lose the ability to walk without assistance and move to the walking with assistance health state
- Type 4 – all patients are in the BRND health state.

Table A6: Best supportive care

Type 1						
Month	**Permanent Ventilation**	**Not sitting**	**Sitting**	**Walking with assis-tance**	**Broad range of normal de-velopment**	**Dead**
6	24.50%	39.90%				35.60%
12	29.90%	27.20%				42.90%
18	33.47%	13.28%				53.25%
24	32.30%	6.47%				61.23%
30	29.41%	3.15%				67.44%
36	26.15%	1.54%				72.31%
Type 2						

Month	Permanent Ventilation	Not sitting	Sitting	Walking with assis-tance	Broad range of normal de-velopment	Dead
6			0%		100.00%	
12			100%			
18			100%			
24			100%			
30			100%			
36			100%			
Type 3						
Month	**Permanent Ventilation**	**Not sitting**	**Sitting**	**Walking with assis-tance**	**Broad range of normal de-velopment**	**Dead**
6			0%		100.00%	
12					100%	
18					100%	
24					100%	
30				100%		
36				100%		
Type 4						
Month	**Permanent Ventilation**	**Not sitting**	**Sitting**	**Walking with assis-tance**	**Broad range of normal de-velopment**	**Dead**
6			0%		100.00%	
12					100%	
18					100%	
24					100%	
30					100%	
36					100%	