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ORIGINAL RESEARCH

Cost-Effectiveness of Newborn Screening for Spinal Muscular Atrophy in England

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ABSTRACT

Introduction: We sought to evaluate the cost-effectiveness of newborn screening (NBS) versus no NBS for 5q spinal muscular atrophy (SMA) in England.

Methods: A cost-utility analysis using a combination of decision tree and Markov model structures was developed to estimate the lifetime health effects and costs of NBS for SMA, compared with no NBS, from the perspective of the National Health Service (NHS) in England. A decision tree was designed to capture NBS outcomes, and Markov modeling was used to project long-term health outcomes and costs for each patient group following diagnosis. Model inputs were based on existing literature, local data, and expert opinion. Sensitivity and scenario analyses were conducted to assess the robustness of the model and the validity of the results.

Results: The introduction of NBS for SMA in England is estimated to identify approximately 56 (96% of cases) infants with SMA per year. Base-case results indicate that NBS is dominant (less costly and more effective) than a scenario without NBS, with a yearly cohort of newborns accruing incremental savings of £62,191,531 and an estimated gain in quality-adjusted life-years of 529 years over their lifetime. Deterministic and probabilistic sensitivity analyses demonstrated the robustness of the base-case results.

Conclusions: NBS improves health outcomes for patients with SMA and is less costly com-

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pared with no screening; therefore, it is a cost-effective use of resources from the perspective of the NHS in England.

Keywords: Cost-effectiveness; Cost-utility analysis; Newborn screening; Nusinersen; Onasemnogene abeparvovec; Risdiplam; Spinal muscular atrophy

Key Summary Points

Implementation of newborn screening for spinal muscular atrophy (SMA) in England is:

- Estimated to identify approximately 56 infants per year, which is 96% of all expected new cases of 5q SMA per year.
- Estimated to save > £62 million over the lifetime of an incident cohort screened in 1 year (approximately 59 newborns with SMA).
- Estimated to increase the quality-adjusted life-years accrued by a yearly cohort of newborns over their lifetime by 529.
- Less costly and more effective than a scenario without NBS, when all factors, including costs and patient outcomes, are taken into consideration.

INTRODUCTION

Spinal muscular atrophy (SMA) is a rare genetic disorder characterized by progressive muscle weakness and atrophy, respiratory failure, and in the most severe cases, death in children younger than 2 years of age [1, 2].

More than 90% of SMA is caused by the loss of the *survival motor neuron 1 (SMN1)* gene from chromosome 5 (5q13) which leads to irreversible degeneration of motor neurons [1]. 5q SMA, hereafter referred to as SMA, is classified into four types, based on age of onset and maximum motor milestones achieved. SMA type 1 is the most common (accounting for 50–60% of cases) [3, 4] and most severe form of SMA, with onset in early infancy. SMA type 1 is characterized by a rapid decline of motor and respiratory function, typically leading to death or permanent assisted ventilation (PAV) before 2 years of age if left untreated [1, 2, 5]. SMA types 2 and 3 are characterized by stalled gross motor development, which causes a spectrum of symptoms such as an inability to stand or walk (type 2), or ambulation loss later in life (type 3) [1, 2]. SMA type 4 represents just < 5% of SMA cases and is the least severe form of the disease, with patients retaining ambulation but with proximal weakness of arms and legs later in life [1]. The severity of the disease is mostly driven by the number of copies of *SMN2*, a nearly identical gene to *SMN1,* from which only a limited amount of SMN protein is produced.

The incidence of SMA is 1 in 10,000 live births [6–9], suggesting that approximately 62 infants are born with SMA per year in England. It is estimated that between 668 and 1336 children and adults are living with SMA in the UK, with a worldwide prevalence ratio of 1–2 people per 100,000 [10].

Novel targeted treatments for SMA can prevent loss of motor neurons soon after birth, thereby preventing disease progression. In the United Kingdom, three disease-modifying treatments (DMTs), onasemnogene abeparvovec, nusinersen, and risdiplam, have been approved and are reimbursed for the treatment of SMA. These DMTs demonstrate promise when administered early, ideally prior to symptom onset, to achieve as close to a functional cure as possible [11–20]. More motor neurons are irreversibly lost with later treatment initiation [1]. Patients with SMA symptoms at the time of treatment will likely require respiratory, nutritional, or musculoskeletal support to maximize functional abilities [13, 17, 18, 21–23].

Early diagnosis of SMA through newborn screening (NBS) enables prompt treatment initiation and is critical for optimizing clinical outcomes for infants with SMA [23–26]. Although some infants identified by NBS are already symptomatic at diagnosis [24, 26, 27], implementing NBS would help all infants at risk for SMA to be identified and treated early,

avoiding delays in treatment and irreversible loss of motor neurons. Treatment of infants with SMA identified by NBS is associated with lower medical costs and societal burden than for those patients diagnosed and treated following symptom onset [28]. NBS for SMA has been introduced or is under consideration in several countries [29–34].

It is important for decision-makers to determine if NBS for SMA offers value for money to the health care system. This evaluation aimed to assess the cost-effectiveness of NBS for SMA and immediate treatment with DMTs compared with a scenario without NBS and symptomatic diagnosis and treatment in England.

METHODS

Population Cohort

A total of 585,195 newborns were included in the model based on the number of live births in England in 2020 [35]. The model compared two population cohorts: NBS (patients identified with SMA who were either symptomatic or presymptomatic at the time of screening) and no NBS (patients with SMA who were symptomatic at the time of diagnosis). This is a cost-utility analysis using published data and it does not contain any new studies with human participants or animals performed by any of the authors. As no new studies with human participants were included in this analysis, Institutional Review Board approval was not required, patient consent to participate was not necessary, and the Declaration of Helsinki 1964 does not apply.

Model Structure and Assumptions

A cost-utility analysis using a combination of decision tree and Markov model structures (Fig. 1) was conducted to estimate the lifetime health effects and costs of NBS compared with no NBS. A decision tree was designed to capture NBS outcomes, and Markov modeling was used to project long-term health outcomes and costs for each patient group following diagnosis. An earlier version of the model was published by Velikanova et al. [33]. The Markov model included the following six health states: within a broad range of normal development (BRND) (A state), walking (B state), sitting (C state), not sitting (D state), PAV (E state), and death. All patients were assumed to be treated in the first 6 months after diagnosis (assumed to be within 6 months, 18 months, and 4 years of age for patients with SMA types 1, 2, and 3, respectively). Infants identified by NBS at risk for SMA were assumed to receive treatment shortly after birth.

Patients in the model entered a specific Markov model health state after the decision tree, depending on diagnosis (demonstrated by M() in Fig. 1). All possible transitions in the Markov model are represented by arrows in Fig. 1. Upon achievement of motor milestones, patients were transitioned to the next health state in the next model cycle, and it was assumed that motor milestone achievement would be maintained in treated patients until death. Untreated patients in the model could lose milestones, such as independent sitting or walking. Based on data from a natural history study in SMA, it was assumed that 24% of patients with SMA type 2 with the ability to sit would lose this milestone between 0.7 and 29.1 years, and 9% of patients with SMA type 3 would lose this milestone between 15.5 and 40.5 years [36]. Of patients with SMA type 3 who were able to walk, it was assumed that 51% would lose this milestone between 2.5 and 65.7 years [36]. Patients could transition to death from any health state [36]. This Markov model has also been used to model long-term outcomes for SMA type 1 in health technology assessment submissions and other publications [33, 37, 38].

A 6-months model cycle was used for the first six cycles, followed by yearly cycles to capture changes in childhood development and milestone achievement. A lifetime time horizon was modeled for the base-case analysis (from birth/treatment initiation to age 100 years), and a discount rate of 3.5% was applied for costs and outcomes.

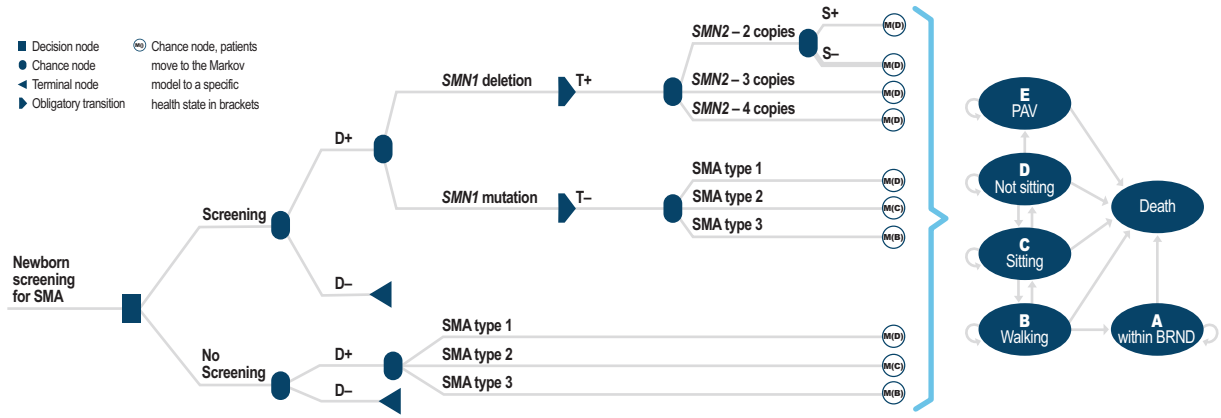

Fig. 1 Two-part model: decision tree (**a**) followed by a Markov model (**b**). *BRND* broad range of normal development; *D+* patients with SMA; *D–* patients without SMA; *NBS* newborn screening; *PAV* permanent assisted ventilation; *S+* symptoms present; *S–* no symptoms; *SMA* spinal muscular atrophy; *SMN* survival motor neuron; *T+* positive test; *T–* negative test.[a]Short-term model [b]Long-term model. Reprinted from Velikanova R, et al. Value Health. 2022;25(10):1696–1704. doi: https://doi.org/10.1016/j.jval.2022.06.010, International Society for Pharmacoeconomics and Outcomes Research, Inc., published by Elsevier Inc. is licensed under CC BY 4.0 (http://creativecommons.org/licenses/by/4.0)

Model Inputs

Model inputs were based on existing literature, local data, and expert opinion.

Patient Distribution

A total cohort of 585,195 infants was included in the model based on the number of live births in England in 2020 [35]. The incidence of 5q SMA is 1 in 10,000 live births [6–9]; homozygous deletion of *SMN1* accounts for

Table 1 Model inputs: treatment patterns

	Onasemnogene abeparvovec	Nusinersen	Risdiplam	BSC
Presymptomatically detected[a] (%)				
SMN2 two copies	93	6	0	1
SMN2 three copies	93	6	0	1
SMN2 four copies	0	6	50	44
Symptomatically detected[a] (%)				
Type 1	56	2	22	20
Type 2	0	10	90	0
Type 3	0	10	90	0
Patients identified via screening but treated symptomatically[a]				
SMN2 two copies	93	6	0	1

BSC best supportive care, *SMN2 survival motor neuron 2* gene
[a]Based on expert opinion

96% of SMA cases, and 4% of cases have a point mutation in *SMN1* [39].

In the model, of infants identified by NBS at risk for SMA who were presymptomatic, it was assumed that 46.7%, 25%, and 28.3% had two, three, or four copies of *SMN2*, respectively [24, 26, 29, 40–44]. Of infants identified by NBS at risk for SMA who were symptomatic, 58%, 29%, and 13% were assumed to have SMA types 1, 2, and 3, respectively [45]. Based on expert opinion, it was assumed that 40% of patients with two copies of *SMN2* became symptomatic by the time they received treatment (before age 6 months). SMA caused by *SMN1* point mutations was assumed to be undetectable because of testing limitations [46].

Treatment Pattern

The proportion of patients with SMA (detected before or after symptom onset) receiving treatment by SMA type and copy number is presented in Table 1.

Clinical Inputs

Short-term efficacy data from relevant clinical trials provided milestone achievements for presymptomatically and symptomatically detected patients, as well as patients identified by NBS but who received treatment following symptom onset, for the first 3 years of the Markov model (Table 2). Because of a lack of available data for presymptomatic infants with four copies of *SMN2*, efficacy data for patients with three *SMN2* copies were applied. For patients identified by NBS but who received treatment following symptom onset, the clinical trajectory of an SMA type 3 patient was used. These assumptions were based on clinical input. Long-term survival data for each health state were extrapolated from existing literature (Table 3).

Resource Use, Cost, and Utilities

The cost of each heel-prick screening test was £4.54 (a Dutch value, which is in line with other sources in Europe, converted to GBP because of lack of UK-specific data) [51]. The confirmatory genetic test was assumed to be £1200, based on prices from Oxford Genetic Laboratories,

Table 2 Model inputs: Short-term efficacy data used for the first 3 years of the Markov model

	Trial[a]
Presymptomatically detected patients	
SMN2 two copies	• SPR1NT (onasemnogene abeparvovec) • NURTURE (nusinersen) • RAINBOWFISH (risdiplam)
SMN2 three copies[b]	• SPR1NT (onasemnogene abeparvovec) • NURTURE (nusinersen) • RAINBOWFISH (risdiplam)
SMN2 four copies[b]	• SPR1NT (onasemnogene abeparvovec) (extrapolated from data for patients with three copies of *SMN2*) • NURTURE (nusinersen) (extrapolated from data for patients with three copies of *SMN2*) • RAINBOWFISH (risdiplam) (extrapolated from data for patients with > 2 copies of *SMN2*)
Symptomatically detected patients	
Type 1	• START, STR1VE-US, and STR1VE-EU (pooled for onasemnogene abeparvovec) • SHINE (nusinersen) • FIREFISH Part 1 and Part 2 (risdiplam)
Type 2	• CS2/CS12 (nusinersen, onasemnogene abeparvovec, and risdiplam)

Table 2 continued

	Trial[a]
Type 3	• CS2/CS12 (nusinersen, onasemnogene abeparvovec, and risdiplam)
Patients identified via NBS but treated symptomatically	• SMA type 3 data from CS2/CS12 (nusinersen, onasemnogene abeparvovec, and risdiplam)[c]

Clinical trials: CS2, NCT01703988; CS12, NCT02052791; FIREFISH, NCT02913482; NURTURE, NCT02386553; RAINBOWFISH, NCT03779334; SHINE, NCT02594124; SPR1NT, NCT03505099; STR1VE-EU, NCT03461289; STR1VE-US, NCT03306277; START, NCT02122952

NBS newborn screening, *SMN2 survival motor neuron 2* gene

[a]The latest long-term follow-up data were also included for the treatment arms where data were available

[b]Because of a lack of available data for patients with four copies of *SMN2*, efficacy data for patients with three copies of *SMN2* were applied

[c]Because of a lack of available treatment-specific data, SMA type 3 trial data for nusinersen were used for all treatment arms, based on clinical input

assuming both gene sequencing and multiplex ligation-dependent probe amplification are needed, based on the test for Duchenne/Becker muscular dystrophy [52]. Treatment and administration costs were based on the UK list prices and the latest National Health Service (NHS) reference costs (2019/2020) [53]. SMA care costs were based on a UK health care resource utilization (HCRU) study updated with 2019/2020 costs [37]. All costs were presented in 2021/2022 GBP values (where required, costs were inflated to 2021 values using Personal Social Services Research Unit's NHS Cost Inflation Index [54]). Utilities were based on published literature and clinical expert input. These were the preferred values used by the National Institute for Health and Care Excellence (NICE) Evidence Review Group in their appraisal of onasemnogene abeparvovec in the United Kingdom [37] and by the Institute for Clinical and Economic Review in the United States (Table 4).

Table 3 Model inputs: long-term efficacy data

Health state	Description	Source[a]
E state	PAV (non-invasive only)	Gregoretti et al. [47]
D state	Not sitting	Kolb et al. [48]
C state	Sitting	Zerres et al. [49]
B state	Walking	General population life expectancy in England, ONS National Life Tables for England 2018–2020 [50]
A state	Walking and within BRND	General population life expectancy in England, ONS National Life Tables for England 2018–2020 [50]

BRND broad range of normal development, *ONS* Office for National Statistics, *PAV* permanent assisted ventilation

[a]For the sitting health state, Wijngaarde et al. [55] was used for sensitivity analysis

Sensitivity Analyses

To assess the robustness of the model and parameters, sensitivity analyses were completed. A deterministic (univariate) sensitivity analysis (DSA) was conducted to evaluate the impact of parameter uncertainty by varying parameter values and reporting the effect on the cost-effectiveness outcomes. The probabilistic sensitivity analysis (PSA) was performed (with 1000 iterations) to assess parametric uncertainty.

Table 4 Model inputs: health care costs and utilities

State	Description	Utility value	References	Health care costs	References
E state	PAV	0.00	Clinical experts	£283,710	UK HCRU costs (2022 update)
D state	Not sitting	0.19	Thompson et al. [56]	£112,500	
C state	Sits unassisted	0.60	Tappenden et al. [57]	£67,567	
B state	Walks unassisted	General population	Ara and Brazier [58]	£8333	
A state	BRND	General population	Ara and Brazier [58]	£414[a]	Assumption

BRND broad range of normal development, *HCRU* health care resource utilization, *PAV* permanent assisted ventilation
[a]Assuming two neurologist visits per year

Table 5 Newborn screening outcomes

Outcome	NBS	No NBS
Number of tests performed	585,254	58.5
1st tier – heel-prick test	585,195	0
2nd tier – confirmatory genetic test	58.5	58.5
Number of cases treated	58.5	58.5
Patients identified and treated presymptomatically	45.8	0.0
Patients identified before symptom onset but treated symptomatically	10.5[a]	0.0
Patients identified and treated symptomatically	2.2[b]	58.5

NBS newborn screening, *SMN1 survival motor neuron 1* gene, *SMN2 survival motor neuron 2* gene
[a]40% of SMA patients with two copies of *SMN2* are assumed to become symptomatic by the time they receive treatment
[b]4% of patients with SMA are assumed to have an *SMN1* point mutation and are thus not detected by qPCR-based newborn screening

Scenario Analyses

The scenario analyses tested key model assumptions and provided an analysis of how robust the base-case incremental cost-effectiveness ratio (ICER) was to key parameters in the model.

The discount rate, time horizon, and analysis perspective (payer and societal) used in the model were assessed in the scenario analyses. Indirect, caregiver, and transportation costs were applied in the societal perspective scenario. Inputs (costs) and assumptions applied are presented in the supplementary material. An additional scenario looked at the impact of informing the survival of C state patients using a more recent natural history study of survival in patients with SMA [55],

Table 6 Base-case results (payer perspective and discounted at 3.5% p.a.)

Strategy	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£ per QALY)
NBS	£160,068,073	1346	1140	–£62,191,531	423	529	–117,541 (dominant)
No NBS	£222,259,604	924	611				

ICER incremental cost-effectiveness ratio, *LY* life-year, *NBS* newborn screening, *p.a* per annum, *QALY* quality-adjusted life-year

although based on a smaller group of SMA patients ($n = 307$ [55] vs. $n = 569$ in the study that informed the base-case analysis [49]).

RESULTS

Newborn Screening Outcomes

NBS is estimated to identify approximately 56 infants per year at risk for SMA, which is 96% of all SMA patients (4% are assumed to have an *SMN1* point mutation that is assumed undetectable by NBS owing to test limitations [39]) in England. We estimate that 46 of these patients will be asymptomatic at the time of treatment, and 10 patients will be symptomatic, even if identified by NBS (Table 5).

Base-Case Results

In the base-case analysis, over the lifetime of a newborn cohort identified (yearly), total costs for NBS versus no NBS were £160,068,073 and £222,259,604, respectively, with an incremental cost savings of £62,191,531 for the NBS cohort (Table 6). The introduction of NBS over the lifetime of a newborn cohort identified per year was associated with total quality-adjusted life-years (QALYs) of 1140 versus 611 for no NBS, thereby providing an incremental gain of 529 QALYs. NBS was associated with 1346 life-years (LY) (vs. 924 with no NBS) and incremental LYs of 423 over the lifetime of a newborn cohort identified per year. Base-case results indicate that NBS is dominant (less costly and more effective) compared with the scenario without NBS, with an ICER of –£117,541 per QALY (Table 6).

To provide further insight into the main drivers of health gains and health care cost savings associated with NBS and early treatment, the proportion of patients in each of the six health states of the model (see Fig. 1) was assessed at different time points to follow children's development over time. The results of this analysis under NBS and no NBS are provided in Figs. S1 and S2 of the supplementary material. With NBS and early treatment, approximately 80% of children with SMA will likely sit and walk independently, as opposed to approximately 20% of children in the current situation, in which no NBS is available, from the age of 5 years old onward.

This difference in motor milestone achievements will lead to a substantially longer and improved quality of life in SMA patients treated early because of NBS, as well as a drastic reduction in costly HCRU over their lifetimes (Table S7 in supplementary material provides economic outcomes per SMA patient), and demonstrates that NBS and early treatment are expected to provide to each patient with SMA on average an additional 32 years at full health when compared with no NBS, where children are treated at symptom onset. Implementation of NBS will also drastically reduce the costs associated with hospital admissions, breathing equipment, and other costly health care services. When also considering the reduction in drug acquisition costs owing to the different treatment patterns used for treating presymptomatic versus symptomatic patients (see Table 1), NBS with early treatment is expected

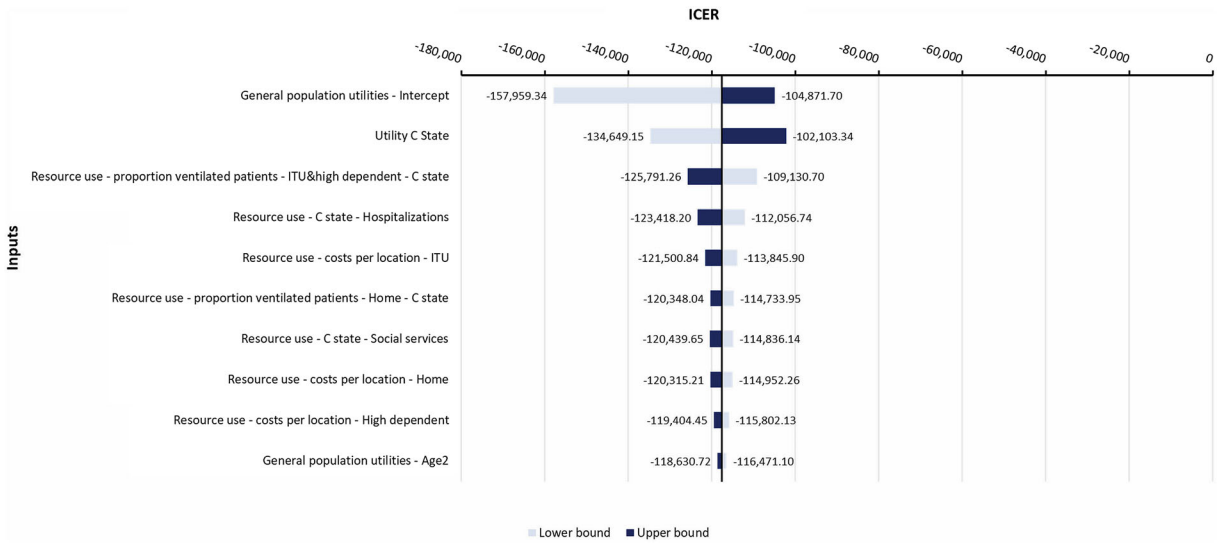

Fig. 2 Deterministic sensitivity analysis. *ICER* incremental cost-effectiveness ratio, *ITU* intensive care unit, *NBS* newborn screening

Table 7 Mean probabilistic results (payer perspective and discounted)

Strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)
NBS	£162,664,662	1131	–£59,318,947	526	–£112,811 (dominant)
No NBS	£221,983,609	606			

ICER incremental cost-effectiveness ratio, *NBS* newborn screening, *QALY* quality-adjusted life-year

to generate a (discounted) cost savings, net of population-level screening costs, of more than £1,000,000 per SMA patient compared with no NBS.

Deterministic Sensitivity Analysis

All DSA results indicated that NBS was dominant versus no NBS (Fig. 2). For all parameters varied in DSA, the ICER was dominant, indicating the robustness of the base-case results. The parameters that had the largest impact on the ICER were the general population utility intercept values, C state utility value, and resource use for ventilated patients in the C state. DSA results for all the other inputs were within ± 4.4% around the base-case result.

Probabilistic Sensitivity Analysis

Results of the PSA are presented in Table 7 and Fig. 3. The PSA indicated that NBS is dominant versus no NBS, with a mean incremental cost of –£59,318,947 and a mean ICER of –£112,811 (Table 7), indicating the robustness of the base-case results. All simulated ICERs fall below willingness-to-pay thresholds of £20,000, £30,000, and £100,000 per QALY (Fig. 3) [59].

Scenario Analyses

Scenario analyses were performed by: (1) varying the discount rate (set to 1.5%), (2) switching lifetime time horizons (using 10 and 50 years, respectively), (3) changing the data source informing the survival for patients in C state [55], and (4) incorporating societal cost in terms of lost productivity for the patients, their

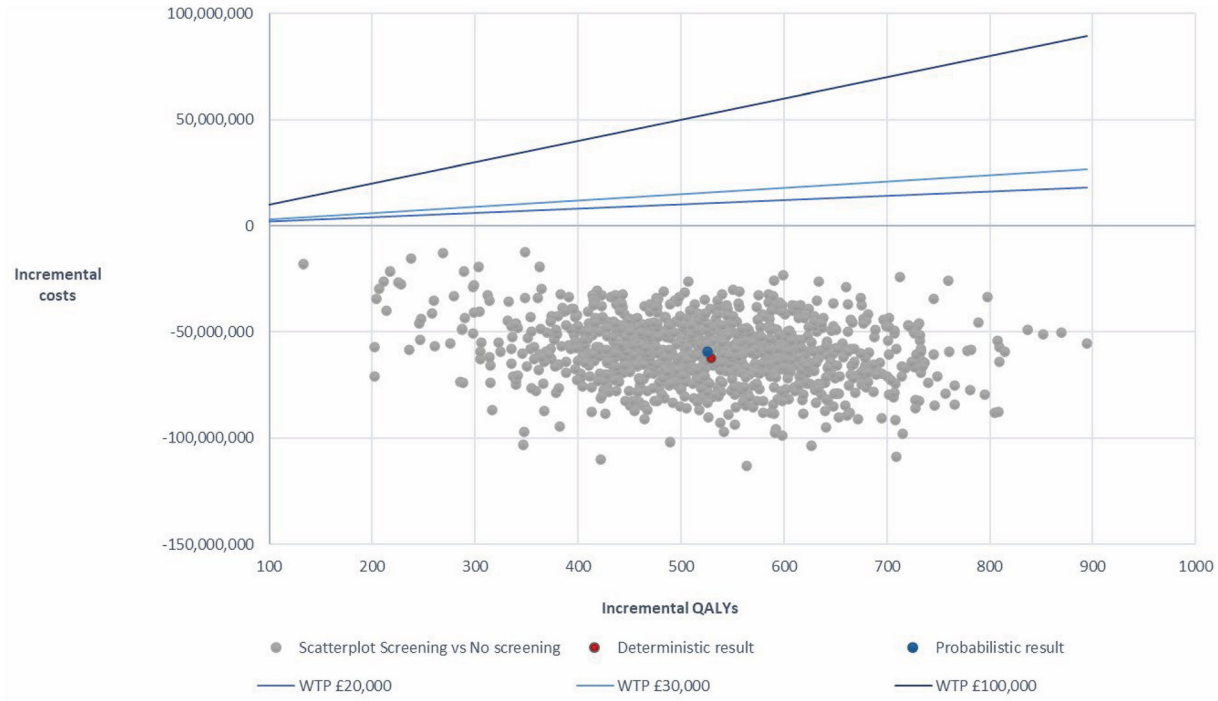

Fig. 3 Incremental cost-effectiveness plane with willingness-to-pay thresholds. *QALYs* quality-adjusted life-years, *WTP* willingness-to-pay

caregivers, and transport costs (societal perspective). All scenario analyses demonstrated that NBS was dominant compared with no NBS (Table 8).

DISCUSSION

In this economic analysis, NBS for SMA for a cohort of 585,195 newborns identified during a single year and followed over their lifetime was associated with a gain of 529 QALYs and savings of £62,191,531 when compared with no NBS in England. This demonstrates that NBS is dominant (less costly and more effective) compared with no NBS. NBS for SMA would be cost-effective and cost-saving compared with no NBS for patients with SMA from the perspective of the NHS.

Infants at risk for SMA identified by NBS achieved more motor milestones, improved lifetime health outcomes, and reduced health care costs compared with patients who were clinically diagnosed after symptom onset; therefore, the costs of NBS on the NHS are fully offset by the cost savings associated with early identification and treatment of infants at risk for SMA.

The DSA and PSA demonstrated the robustness of the model and validated the cost-effectiveness outcomes, indicating that NBS for SMA is cost-saving for all variations in the sensitivity and scenario analyses. In addition, this model was built on the same Markov structure and applied key assumptions used in the model assessing the cost-effectiveness of onasemnogene abeparvovec for SMA type 1, which has been accepted by NICE [37], and other published SMA models [33, 38, 60, 61].

This analysis was performed based on the estimated live births in England; however, including other nations of the United Kingdom, i.e., Wales, Scotland, and Northern Ireland, would not affect the overall result that NBS for SMA would be a cost-saving health care utilization for the respective NHS. Cost-effectiveness models have been conducted in several other countries, including from the Dutch payer perspective, and have also demonstrated

Table 8 Scenario analysis results

Strategy	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£ per QALY)
Discount rate of 1.5%							
NBS	£211,956,043	2265	1924	–£98,065,394	920	1006	–£97,485 (dominant)
No NBS	£310,021,437	1345	918				
Lifetime time horizon of 10 years							
NBS	£108,267,465	449	339	–£4,778,101	49	105	–£45,567 (dominant)
No NBS	£113,045,566	401	234				
Lifetime time horizon of 50 years							
NBS	£151,618,768	1192	1016	–£61,117,353	314	440	–£139,009 (dominant)
No NBS	£212,736,121	878	577				
C state survival based on Wijngaarde et al. [55]							
NBS	£162,528,089	1365	1152	–£108,623,888	211	402	–£270,023 (dominant)
No NBS	£271,151,977	1154	749				
Societal perspective							
NBS	£166,772,287	1346	1140	–£78,876,005	423	529	–£149,074 (dominant)
No NBS	£245,648,292	924	611				

ICER incremental cost-effectiveness ratio, *LYs* life-years, *NBS* newborn screening, *QALYs* quality-adjusted life-years

the cost-effectiveness of NBS for SMA [33]. Adoption of NBS in the European Union [29] and in the rest of the world [30] is rapidly expanding. For example, approximately 85% of newborns are screened for SMA in the United States [62]. The findings of this economic analysis provide a strong rationale for the introduction of NBS for SMA in England.

Data limitations of the study were mitigated by extrapolating efficacy and survival data. Applying parametric survival extrapolation to estimate long-term patient survival carries a high degree of uncertainty. To verify the survival curves, expert opinion was applied, and the most conservative survival parameters were chosen for the base-case results.

Efficacy was extrapolated from presymptomatic studies, which included patients who were identified via NBS or clinical diagnosis after symptom onset (no NBS). Considering this, we have estimated that approximately 40% of patients with two copies of *SMN2* would be symptomatic at the time of treatment initiation.

The model does not take into consideration the diagnostic journey of patients following symptom onset. A recent Italian study has demonstrated a delay between first symptoms and diagnosis of SMA of 1.94, 5.28, and 16.8 months for patients with SMA types 1, 2, and 3, respectively. This journey included several medical consultations and other examinations, such as magnetic resonance imaging, electromyography, or muscle biopsy. Considering these potential additional costs of diagnosis would result in an even more favorable scenario for NBS [63].

In the model, patients with four copies of *SMN2* were considered equal to patients with three copies of *SMN2* in terms of costs and outcomes, because data for patients with four *SMN2* copies treated at birth are critically lacking and no comparison exists for patients treated after symptom onset versus untreated patients. Therefore, we adopted a conservative approach and considered these patients similar to patients with three copies of *SMN2*.

Although the published consensus is to treat patients with four copies of *SMN2*, several countries have adopted a "watch and wait" strategy for these patients. A recent study demonstrated that the economic benefits of NBS for patients with four copies of *SMN2* were substantially less than for patients with three copies [28]. From a clinical perspective, however, recent data from Germany demonstrated that five of seven patients with four copies of *SMN2* may develop irreversible symptoms of SMA before the age of 4 years [64]. It must be noted that *SMN2* copy number quantification is not entirely standardized and that significant inter- [65] or intra- [66] laboratory differences may be observed, especially for the higher copy numbers. Nevertheless, it is very unlikely that this would significantly alter the conclusion of this model or other health economic assessments because different studies converge to demonstrate a similar percentage of copy numbers in the SMA subpopulation.

More research is needed to identify long-term costs for surviving patients, specifically the costs associated with the walking and sitting health states. In the model, for all available treatment options, the same costs were applied per health state to avoid bias towards any of the treatments. The sensitivity of final economic outcomes to the magnitude of resource use costs by health states was evaluated in deterministic sensitivity analysis (see Fig. 2), which indicated in all cases NBS as a dominant option over clinical diagnosis (no NBS).

CONCLUSION

Based on all data available and conservative assumptions, we have demonstrated that NBS for SMA is cost-effective in England. Including SMA in the official screening program will not only result in increased longevity and health-related quality of life for affected patients but also in very substantial cost-savings for the NHS. This finding strongly supports the inclusion of SMA in the official NBS program in England.

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