# Cost-effectiveness of spinal muscular atrophy newborn screening based on real-world data in Belgium

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# Abstract (200 mots)

Objective: To assess the cost-effectiveness of spinal muscular atrophy (SMA) newborn screening (NBS) followed by disease-modifying treatment with no SMA NBS and delayed disease-modifying treatment.

Method: A previously SMA treatment model was adapted to estimate the lifetime cost-effectiveness of the SMA NBS followed by treatment compared to treatment without NBS from the Belgian healthcare perspective. Real-world data, including quality of life, costs, and motor development data, were collected on 12 SMA patients identified by NBS, and 43 patients identified by their symptoms. Deterministic and probabilistic sensitivity analyses were conducted to test the robustness of the analysis.

Results: SMA NBS was associated with slightly higher healthcare costs (€ 6,858,061 vs. € 6,738,120) but more quality-adjusted life years (QALY) (40.95 vs. 20.34) compared to treated SMA without NBS, leading to an incremental cost-effectiveness ratio of € 5,820 per QALY gained. SMA NBS was dominant from a societal perspective (incremental costs € - 14,457; incremental QALY = 20.61), when incorporating the burden on caregivers (incremental costs = € - 74,353; incremental QALY = 27.51), and when the treatment was chosen by the parents (incremental costs = € - 2,596,748; incremental QALY = 20.61).

Conclusion: This study reveals that SMA NBS coupled with early treatment is cost-effective compared with delayed treatment and was dominant (i.e., lower costs, more QALY) when societal perspective, caregiver burden, and treatment based on parental preference were considered.

# Short Title:

Cost effectiveness of real-world SMA NBS

# What this paper adds

- We need to assess the cost-effectiveness of SMA NBS to implement it more broadly.

- We used real-life data to evaluate the costs and utility of late-treated SMA patients and those treated after NBS.

- SMA NBS coupled with early treatment is cost-effective compared with delayed treatment and was dominant when societal perspective, caregiver burden, and treatment based on parental preference were considered.

# Abbreviation

ICER: Incremental cost-effectiveness ratio

NBS: Newborn screening

PSA: probabilistic sensitivity analysis

QALY: Quality-adjusted life years

SMA: Spinal Muscular Atrophy

# Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive disorder that affects 1 in 10,000 newborns 1,2. In its most common and severe form, SMA1, which accounts for about 60% of cases, 93% of children die before the age of two years in the absence of supportive treatment 3. Those who survive present with severe motor impairment, as they are unable to hold a sitting position. In the intermediate form of the disease, SMA2, children can sit but cannot stand or walk. In the “milder” form, SMA3, patients may lose their ability to walk in adolescence or adulthood or have their walking range restricted. SMA is associated with substantial healthcare and societal costs and has a major impact on the quality of life of patients and their caregivers 4. A recent systematic review revealed that the average annual cost of SMA1, in which symptoms appear before the age of 6 months, ranged from US$75,047 to $196,429 per year. The annual costs of the later-onset forms range from US$27,157 to US$82,474 per year 5.

Since 2016, three disease-modifying treatments have been approved. They all reduce infant mortality in SMA1 and improve motor functions in patients with all types of SMA 6. The benefits in terms of motor improvements are strongly linked to the time of treatment initiation, with maximal benefits associated with treatment prior to onset of symptoms 7. To be able to treat as early as possible and therefore maximize treatment efficacy, newborn screening (NBS) programs have recently been initiated in several countries 8,9. In Belgium, the NBS program was begun in March 2018 and to date (March 2023), more than 250,000 newborns have been screened, and 19 were identified and treated rapidly 10,11.

The implementation of an NBS program comes with costs that are added to the already significant cost of treatment. It is therefore important to carry out an economic evaluation to assess the cost-effectiveness of NBS for SMA. Economic evaluations are increasingly used by decision makers to efficiently optimize scarce healthcare resources. Some cost-effectiveness analyses of NBS SMA have been conducted 12–16, and these suggest that NBS is a highly cost-effective intervention. Existing studies were based on simulation models that used efficacy data from clinical trials rather than real-life NBS SMA data. This may result in a significant bias, as patients in clinical studies are selected according to strict inclusion and exclusion criteria. The early initiation of the ongoing Belgian SMA NBS program has allowed us to assess the cost-effectiveness of SMA NBS followed by a disease-modifying treatment (nusinersen, onasemnogene abeparvovec, or risdiplam) compared with no SMA NBS and delayed disease-modifying treatment.

# Methods

## Model structure

An economic model was used to compare the costs and outcomes, expressed in quality-adjusted life years (QALYs), for two groups of SMA patients: those identified by symptoms and those identified by NBS. Real-life data from observational studies in Liege (Belgium) were collected between 2018 and 2022 for patients in these groups. The first group included 43 SMA patients treated with a disease-modifying drug after clinical diagnosis with symptom onset (referred to as the symptomatic-treated group). These subjects were treated beginning at 2.5 months of life or later. The second group of 12 patients were not identified by symptoms (NIS group). These subjects were identified through the NBS program and treatment began before 55 days.

A previously validated model used by the Institute for Clinical and Economic Review to analyze the cost-effectiveness of nusinersen and onasemnogene abeparvovec for treatment of SMA in the US17,18 was adapted to estimate the cost-effectiveness of NBS. The model was developed using Microsoft ® Office Excel 2022. The model used monthly cycles and included five different health states: permanent ventilation, not-sitting, sitting, walking, and death. The model consisted of two parts: (1) a short-term model (30 months) using the actual data from the study in Liege where patients all started in the non-sitter state and the age of acquisition of sitting or standing was reported for each patient individually, and (2) a lifetime extrapolation model. The motor function milestones achieved at the end of the short-term model were assumed to be maintained until death, thus, NIS patients who were walking at 30 months of age were expected to maintain the ability to walk. The long-term model involved extrapolation of motor milestones (estimated be the same that at the end of the short-term model), permanent ventilation, and mortality. The long-term mortality risk associated with each health state was modeled by fitting survival curves to data estimated by a disease specialist for each health state. Based on expert opinion and literature 19, mortality for walkers and sitters was assumed to be the same as for the general population 20 (81 years), whereas the mean life expectancy for non-sitters was set at 20 years and that for patients with ventilation was set at 5 years. Figure 1A illustrates the model.

*Figure 1*

In line with the Belgian guidelines for economic evaluation, a discount rate of 3% for costs and 1.5% for utility values were used 20. There is no threshold for cost-effectiveness in Belgium 28. In Europe, only the UK (€24,000-36,000), Poland (3 times per capita GDP, about €40,000), Netherlands (€ 20,000 – 80,000), and Slovakia (24-35 average salaries, i.e., €18,000-27,000) have explicit thresholds. Several other countries have an implicit threshold, which is usually between two- and three-times GDP per capita (Hungary).

## Model inputs

#### Patient characteristics

Data on motor function milestones, permanent ventilation, and mortality at different time points were extracted from the observational studies performed in Liege. There were two distinct populations: (1) the symptomatic-treated group of SMA patients identified by their symptoms who began to be treated after 2.5 months (n=43) and (2) the NIS group of SMA patients identified by NBS who were treated before the age of 2 months (n=12). Only patients aged more than 18 months were included in order to have a sufficient understanding of maximum motor level acquired. None of the patients were on permanent ventilation. Individual patient characteristics are given in supplementary file 1.

#### Data collection

Patients or their caregivers completed a questionnaire that included sociodemographic (age, occupation) and medical questions (motor assessment, age at symptom onset, diagnosis, and treatment initiation and type). Financial costs were collected from responses to a cost questionnaire containing questions about direct medical and non-medical costs and indirect costs over the past year.

### Utility values and cost data

Utilities were derived from Health Utilities Index 2. Utility decreases with age, and this was taken into account. Utility values were estimated at 0.32, 0.51, and 0.78 for symptomatic-treated non-sitters, sitters, and walkers, respectively; and the utility value for NIS patients was 0.96 24. Costs and utility values of NIS patients and symptomatic-treated walkers differed, as the latter have reduced walking perimeter and difficulty in climbing stairs. Difficulties walking have a strong impact on utility values and costs partly due to additional needs (such as physiotherapy). We estimated from real world studies22,23 that about 40% of patients with two copies of *SMN2* who were treated early would have utility values and costs comparable to SMA3 patients. This represents 20% of NIS patients in the cohort. In terms of cost and utility, we therefore assumed that 20% of NIS patients would have outcomes equivalent to symptomatic-treated walkers.

In the base-case analysis, the costs were based on the Belgian guidelines for economic evaluation and included hospitalization, consultation, treatment, treatment administration costs, and NBS costs. Healthcare costs were derived from various sources including patients and caregivers, financial departments of the hospital, and the Institut National d'Assurance Maladie-Invalidité (the Belgian social security organization that pays for these services) 25. We first measured the needs in terms of specialized consultations (doctors, physiotherapists) and specific equipment (ventilators) using questionnaires and analyses of patients' medical files. Then, we evaluated the costs using the Belgian social security costs as well as the costs provided by the hospital, enabling us to calculate costs for each individual patient.

The costs of treatment by disease-modifying therapies included the official cost of the treatment itself, the cost of hospitalization for treatment administration if applicable, and the medical consultation directly related to treatment delivery (Table 1). The cost of the treatment is that provided by the Belgian social security. In our population, patients used one of three available treatments: nusinersen, onasemnogene abeparvovec, or risdiplam (Figure 1B). We took the percentage of patients treated in each category by each treatment and multiplied it by the cost of the respective treatment. The proportion of use of each treatment was not identical between populations. For example, NIS patients, who were younger than symptomatic-treated patients, were more likely to have been treated with onasemnogene abeparvovec, which has a marketing authorization based on patient weight. The frequency of administration is different for each treatment. In addition, five patients had their treatment as part of a clinical trial or treatment was funded through a compassionate use policy and therefore received the treatment at no cost. However, we included the costs of the treatments as if they had been paid. In 2018, only nusinersen had been approved for use in Belgium. Onasemnogene abeparvovec has been reimbursed since 1 December 2021 and is available for non-symptomatic patients if they have two or three copies of *SMN2*. Since then, five patients with two or three copies of *SMN2* were identified through NBS, and all were given onasemnogene abeparvovec.

The Office of Birth and Childhood (Office de la Naissance et de l’enfance – ONE) incurs the costs related to the implementation and operation of NBS. In order to estimate the cost per identified patient, we divided the number of children screened by the number of children identified to calculate how many children must be screened to identify one patient with SMA. Since the cost of the test is €5 per child screened, this represents a cost of €66,667 for identification of one child.

Table 1 presents the total costs and utility values for patients with SMA in the NIS group and for patients in the symptomatic-treated group based on motor milestone reached.

*Table 1*

## Results and sensitivity analyses

Incremental costs and QALYs were used to calculate the incremental cost-effectiveness ratios (ICERs) of symptomatic-treated versus NIS patients. To assess the robustness of the analysis, various scenarios and probabilistic sensitivity analyses were completed. The following scenarios were considered: Scenario S1 used the societal perspective (including non-medical costs). Scenario S2 reflects caregiver burden (including healthcare costs, non-medical costs, parents’ loss of productivity, and impact on the quality of life of the caregiver). For scenario S3, treatments were distributed based on the percentages of patients in our cohort treated with each approved drug. It should be noted that this exercise does not reflect reality as the accessibility of the treatment is influenced by marketing authorizations (e.g., onasemnogene abeparvovec is limited to patients with two or three copies of *SMN2* who weigh under 12 kg and risdiplam can only be used to treated patients who are older than 2 months). Scenario S4 considered the preferences of parents for the treatment of NIS children based on the recent work of Deng et al. 26. This study reported the choices of 18 sets of parents whose child had been diagnosed with SMA following NBS. Of these 18 children, thirteen (72%) were given onasemnogene abeparvovec, two (11%) risdiplam, one nusinersen (5%), and two (11%) did not receive any treatment by choice of the parents. In Belgium, all patients would be treated, even if they had four copies of *SMN2*. We therefore allocated the percentage of untreated subjects to the risdiplam group. In this scenario, 5.6% of NIS patients would be treated with nusinersen, 72.2% with onasemnogene abeparvovec, and 22.2% with risdiplam, and the allotment of symptomatic-treated patients to treatment groups was the same as in this study. Scenario S5 used a 10-year time horizon for (A) healthcare perspective, (B) societal perspective, and (C) societal perspective plus caregiver burden. Scenario S6 used a 3% discount rate for both costs and QALYs. Finally, scenario S7 used alternative survival estimates for the healthcare perspective with a survival for non-sitter of (A) 30 years or (B) 40 years. A probabilistic sensitivity analysis (PSA) was performed by varying all model parameters using 1,000 simulation runs. Due to the limited amount of data, a mean value of ± 20% was used in the PSA for the distribution of costs and utility values. Results of the PSA were evaluated in the cost-effectiveness plane and in the form of a cost-effectiveness acceptability curve, which demonstrated the probability that SMA NBS is cost-effective based on decision-makers willingness to pay per QALY gained.

# Results

From the healthcare perspective, NIS patients cost about €120,000 more than symptomatic-treated patients. Those patients identified and treated early had 20.61 additional QALYs over a lifetime, resulting in a cost per QALY gained of €5,820 (Table 2).

*Table 2*

The results of the sensitivity analyses are presented in Table 2. In several scenarios, NBS for SMA resulted in lower costs per QALYs. The scenarios where SMA NBS was cost-effective included those when the societal perspective was included (S1), when caregiver burden was included (S2), when treatment was selected by parents (S4), and when alternative survival estimates were employed (S7). In all deterministic sensitivity analyses, the ICER was below €60,000 per QALY gained, and, therefore, NBS could be considered as cost-effective. The cost-effectiveness was especially sensitive to the societal perspective and the choice of the treatment. The PSA are illustrated in Figure 2 and Figure 3. This analysis suggested that NBS has a 100% probability of being cost-effective from a threshold of €20,000 per QALY gained.

*Figure 2*

*Figure 3*

# Discussion

We performed a cost-effectiveness analysis of NBS for SMA using real-life data from Belgium obtained on subjects identified by NBS or by symptoms who were treated and follow for up to 30 months. Our analysis revealed that SMA NBS had nearly similar healthcare costs to symptomatic treatment with a large gain in QALY. NBS SMA is therefore cost-effective compared to treat SMA without NBS, with a cost per QALY gained of €5,820. This result is in line with other studies that reported the cost-effectiveness, and even dominance, of NBS SMA compared to no screening. Indeed in Australia12, in the Netherlands15, and in the UK16, SMA NBS was associated with lower total healthcare costs than no screening. These studies, however, were not based on real life data but rather on data from clinical trials and did not include motor function data or information on preferences of parents for type of treatment. Except in the UK, NIS patients included were strictly non-symptomatic at the start of treatment, which is not always the case in real life. To our knowledge, this study is therefore the first to include real-life data. Our study is based on data collected in Belgium, one of countries to launch an SMA NBS program, beginning in 2018.

Deterministic sensitivity analyses indicated that NBS was cost-effective in all scenarios and was dominant in several: (1) when treatment was based on parents’ preferences, (2) when a societal perspective was considered, and (3) when caregiver burden was incorporated. Although societal perspective and caregiver burden are not part of the Belgian guidelines for economic evaluation, many other countries do take these aspects into consideration.

Although cost-effectiveness analyses are mandatory for drug reimbursement decisions, they are not yet required by the health authorities for public health program even if the concept of cost is part of the initial criteria for implementation of NBS29-31. When submitting a reimbursement to health authorities, a budget impact analysis is often included, which estimates the implications in terms of annual budget over a period of three to five years. This requires estimating the impact of the NBS, which includes the cost of screening (based on the total number of babies screened), the cost of treatment for those screened, and any reduction in costs for due to pre-symptomatic diagnosis of disease. The cost of case finding, including diagnosis and treatment of diagnosed patients, must be economically balanced against the possible expenditure for medical care as a whole.

The cost-effectiveness of NBS has been confirmed for various diseases. For instance, the cost-effectiveness of an expanded NBS program compared to the previous standard screening (27 diseases versus 7 previously) was established in Texas in an analysis conducted on hypothetical cohorts in 200732. Results of the study indicated that patient outcomes were improved by preventing morbidity and mortality of treatable disease and found that the population tested had more QALYs than the non-tested population. Although the decision to include new diseases in the NBS panel did not depend on the results of the study, the study supported the policy decision to expand the NBS program. Since 2007, the Texas NBS program has been expanded from testing for 27 to 57 diseases. NBS for severe combined immunodeficiency was demonstrated to be cost-effectiveness in studies conducted in the US (from $27,907 to $53,560 per QALY gained)33 and in the Netherlands(based on literature data, €33,400 per QALY earned)34. Efficacy data that show the value of early treatment of SMA and early encouraging results in other rare diseases for which therapies may soon be available such as Duchenne muscular dystrophy35 Angelman’s syndrome36 and other neurological conditions37 strongly suggest that NBS programs should be poised to expand in response to therapeutic development.

Our study has several limitations. First the NBS for SMA was implemented in Belgium only five years ago, and annual birth rate in Southern Belgium is about 50,000 per year. As a consequence, during the time frame of our study only 250,000 subjects were screened, and only 19 infants were diagnosed with SMA. Further, patients with short follow-up were not considered. Thus, there remains uncertainty about the consequences of treatment including the motor evolution of the patients and their survival. We used motor function milestones to define general health states and assumed relationships between health states and survival. The long-term effects of the currently used treatments are unknown. In line with expert opinion, the base case analyses assumed that these milestones are maintained until death. Although there is no evidence that patients will regress following disease modifying treatment 27,38, given the lack of long-term follow-up of treatment efficacy and utility data, a registry of SMA patients should be created, and patients should be followed to allow economic evaluations with additional real-life data. Finally, the cost of the diagnostic journey for patients identified by symptoms, which includes useless magnetic resonance imaging, electromyography, or gene testing, was not included in this study39. Inclusion of these expenses would marginally increase the cost-effectiveness of the NBS. In conclusion, SMA NBS coupled with one of the three available treatments leads to substantial better health outcomes, demonstrating the cost-effectiveness of NBS compared to delayed treatment in real-life settings.

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# Supporting information

Table 1: Costs for approved SMA treatments and utility values and costs for treatment of NIS and symptomatic-treated subjects.

Table 2: Cost-effectiveness of SMA NBS in different scenarios.

Figure 1: A. Schematic of the model used for analysis of cost-effectiveness of SMA NBS. B. Schematic of patient treatment. No NBS: symptomatic-treated; OA: onasemnogene abeparvovec.

Figure 2: Incremental cost-effectiveness plane.

Figure 3. Cost-effectiveness of NBS versus no NBS in base-case scenario.

Supplementary file 1: Evolution of patients in short-term model

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| --- | --- | --- | --- | --- |
| **Treatment** | **Treatment cost** | **Administration cost a** |  |  |
| Nusinersen | €88,300 *per injection (6 in first year and 3/year thereafter)* | €255 *per injection* |  |  |
| Onasemnogene abeparvovec | €1,873,000 *(only one injection)* | €2,989 *per injection* |  |  |
| Risdiplam | €289,000 *(per year)* | €408 *per year* |  |  |
| NBS | €5 *per child* | €66,667 *per identified 1 child* |  |  |
|  | **Healthcare costs (per year)** | **Non-medical costs (per year)** | **Parents productivity loss (per year)** | **Utility cost** |
| NIS – not symptomatic | €1,807 | €0 | €1,702 | €0.965 |
| Symptomatic-treated – non-sitter | €32,153 | €6,385 | €23,236 | €0.32 |
| Symptomatic-treated – sitter  | €13,132 | €6,800 | €3,405 | €0.51 |
| Symptomatic-treated – walker and NIS –symptomatic | €8,725 | €10,000 | €2,979 | €0.78 |

*Table 1: Costs for approved SMA treatments and utility values and costs for treatment of NIS and symptomatic-treated subjects.*

a Administration costs include hospitalization, consultation, and examination costs.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **Total Costs** | **Life-years gained** | **QALYs gained** | **ICER****Cost / QALY gained** |
|  | **Populationa** |
| Base case | NIS | €6,858,061 | 46.80 | 40.95 | €5,820 |
| Post | €6,738,120 | 35.80 | 20.34 |
| S1: Societal perspective  | NIS | €6,905,202 | 46.80 | 40.95 | Dominatedb |
| Post | €6,919,659 | 35.80 | 20,34 |
| S2: Societal perspective + caregiver impacts  | NIS | €6,973,382 | 46.80 | 43.07 | Dominated |
| Post | €7,047,735 | 35.80 | 15.56 |
| S3: Distribution of treatments with the same proportion in NIS and Post patients (health care perspective) | NIS | €6,661,517 | 46.80 | 40.95 | €57,749 |
| Post | €5,316,196 | 35.80 | 20.34 |
| S4: Distribution of treatments according to parental choice | NIS | €3,786,492 | 46.80 | 40.95 | Dominated |
| Post | €6,383,240 | 35.80 | 20.34 |
| S5A: Healthcare perspective with a 10-year time horizon | NIS | €2,354,936 | 9.30 | 8.04 | €10,644 |
| Post | €2,283,005 | 8.63 | 4.39 |
| S5B: Societal perspective with a 10-year time horizon | NIS | €2,485,055 | 9.30 | 8.04 | Dominated |
| Post | €2,492,976 | 8.63 | 4.39 |
| S5C: Societal perspective + caregiver impacts with a 10-year time horizon | NIS | €2,511,543 | 9.29 | 8.26 | Dominated |
| Post | €2,566,622 | 8.62 | 3.12 |
| S6: Base case with same discount rate (3%) | NIS | €6,858,061 | 30.54 | 26.95 | €8,856 |
| Post | €6,738,120 | 23.95 | 13.41 |
| S7A – alternative survival estimates (30 year) | NIS |  €6,858,061  | 46.80 | 40.95 | Dominated |
| Post |  €6,913,453  | 35.80 | 20.57 |
| S7B – alternative survival estimates (40 year) | NIS | €6,858,061  | 46.80 | 40.95 | Dominated |
| Post |  €7,106,953  | 35.80 | 20.84 |

*Table 2: Cost-effectiveness of SMA NBS in different scenarios.*

*a Post indicates subjects identified based on symptoms.*

*b”Dominated” means here a negative cost*