# Cost-effectiveness analysis of Onasemnogene Abeparvovec-xioi (Zolgensma®) and best supportive care treatment for Spinal Muscular Atrophy I in the Netherlands with early-treatment scenario

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# Abstract

**Background**: Spinal muscular atrophy (SMA) is an inherited neuromuscular disorder and is considered one of the most common genetic causes of infant mortality. Onasemnogene Abeparvovec-xioi (OA) (Zolgensma®) is a gene therapy showing promising health outcomes for SMA treatment, with a list price of approximately €2,000,000. This study aims to provide a cost-effectiveness analysis in the Netherlands for the treatment of SMA type I with OA with newly published data that can guide decision-makers in the Netherlands when it comes to determining reimbursement policies.

**Methods**: A Markov model with five health states was replicated to analyze the costs and outcomes for patients diagnosed with SMA Type I. The analysis was conducted from a societal perspective in the Netherlands over a time period of 99 years. Various data sources such as recent clinical trials, published literature, parametric distributions, and Dutch registries, were used to determine the model parameters. Both one-way and probabilistic sensitivity analyses were conducted to assess the uncertainties associated with the model's parameters. Additionally, a scenario analysis was performed to evaluate the potential benefits of early treatment.

**Results**: The base-case incremental cost-effectiveness ratio (ICER) of OA was €257,717 per quality-adjusted life year (QALY) compared to best supportive care (BSC). The ICER of OA from the early treatment scenario was €127,107 compared to BSC. Both are above the Dutch willingness-to-pay (WTP) reference value of €80,000. The key drivers influencing the ICERs were the costs of OA treatment and utility and cost values of 'sitting independently' health state.

**Conclusion**: Based on this model, treatment with OA supports the notion that it offers significant improvements in disease progression, motor skills, and quality of life compared to BSC. A reduced ICER of almost 27% is observed compared to the health technology assessment conducted by the Dutch Health Care Institute. However, it is not cost-effective under the Dutch WTP threshold. The limited availability of clinical trial data, characterized by small sample sizes and short follow-up periods, causes great uncertainty. It is recommended that decision-makers find a suitable balance between these uncertainties and the cost they are willing to pay for the treatment of rare diseases.

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# 1. Introduction

Spinal Muscular Atrophy (SMA) is a rare genetic disorder that affects the neuromuscular system and causes progressive muscle weakness, leading to respiratory failure and death in severe cases[1,2]. The disease affects approximately 1 in 11,000 live births (about 500 new cases per year) and is caused by mutations in the survival motor neuron (SMN) 1 gene. The SMN1 gene turns into the SMN2 gene, which leads to the loss of motor neurons in the brainstem and spinal cord[1–5].

The severity of SMA can vary widely and is linked to the number of copies of the SMN2 gene[6]. SMA is categorized into four main types (type I-IV) based on the age of onset, severity, and clinical characteristics, with type I being the most severe form, also known as Werdnig-Hoffmann disease[6]. Typically, SMA type I manifests within the first six months of life. Infants with type I SMA experience significant muscle weakness, limited head control, and difficulty with swallowing and breathing. Their life expectancy is generally limited to a few years, even with the best supportive care (BSC), whereas patients with type II and III SMA can survive beyond 20 years[7]. Approximately 60% of individuals diagnosed with SMA are classified with type I[1,2,6–10].

Historically, treatment options for SMA (type I) have been limited, with BSC as the primary approach. Nevertheless, the recent development of novel medicines like nusinersen (Spinraza®) and onasemnogene abeparvovec-xioi (OA) (Zolgensma®) have provided new hope for individuals with this devastating disease[11,12]. The Food and Drug Administration (FDA) approved nusinersen in 2016 as the first therapy for SMA[12]. Clinical trials have shown that treatment with nusinersen can improve motor function, increase survival, and delay the need for permanent ventilation in infants with SMA type I[2,13]. OA, a new genetic replacement therapy for SMA, was approved by the FDA in 2019[11]. In 2020 OA was granted market authorization by the European Commission[14]. Results have shown that OA could potentially be more effective than nusinersen[15].
OA is a one-time intravenous infusion of a viral vector that delivers a functional copy of the survival SMN1 gene to motor neurons. This restores the production of the SMN protein, which is crucial for muscle function[16]. Clinical trials have demonstrated that OA can enhance motor function, extend survival, and reduce the need for respiratory support among infants with SMA type I[17–19]. The main advantage of gene therapy is that it requires only a single administration, reducing the burden on patients[20].
Unfortunately, the recent advancements in treatments for SMA are often associated with high costs, posing challenges for both patients and healthcare systems[21–24]. The cost of a single infusion with OA for SMA treatment is estimated to be around €2 million, known as one of the most expensive drugs in the world[25]. The incredibly high costs have prompted an ongoing discussion if the health benefits of OA treatment outweigh the costs and whether OA should be eligible for reimbursement[26–29]. Various cost-effectiveness analyses have been carried out to evaluate the value of OA compared to standard-of-care approaches, such as BSC and nusinersen for SMA type I. It shows that OA offers clinical advantages, but there remain uncertainties regarding its long-term effectiveness. Moreover, the incremental cost-effectiveness ratios (ICERs) associated with OA exceed the threshold value for willingness to pay (WTP)[21,22,27].

The Dutch Health Care Institute (Zorginstituut Nederland (ZIN)) conducted a comprehensive evaluation known as a health technology assessment (HTA) to assess the use of OA for the treatment of SMA type I[28]. The HTA concluded that OA is effective and substantially improved compared to the standard-of-care treatment for SMA type I. However, considering the high cost associated with the OA treatment, the HTA recommended conditional reimbursement with a price arrangement. As of July 2021, OA has been granted conditional reimbursement for the treatment of SMA type I in the Netherlands. This means that the manufacturer of OA has agreed to offer the treatment at a reduced price for a limited period while further evidence is gathered to support its long-term effectiveness[28].

New follow-up data from clinical trials have recently been published of patients diagnosed with SMA type I treated with OA[18]. This newly available data provides more accurate information regarding the survival rates and improvements in motor milestones among patients who received OA treatment compared to the data utilized by ZIN and other previously published cost-effectiveness analyses. As a result, these more accurate insights strengthen the evidence supporting the potential benefits of OA treatment for patients with SMA type I and enhance its role in guiding decisions related to cost-effectiveness. Furthermore, recent publications have introduced another clinical trial, the SPR1NT trial, which has presented promising findings regarding treating pre-symptomatic patients diagnosed with SMA type I[30]. These results contribute to the growing evidence supporting potential therapeutic approaches for this patient population.

The primary objective of this study is to conduct a comprehensive cost-effectiveness analysis of treating SMA Type I patients with OA compared to BSC from a societal perspective in the Netherlands with an early-treatment scenario. The research will incorporate direct costs, such as drug expenses and healthcare resource utilization, and indirect costs, including productivity loss and other out-of-pocket costs. Additionally, the study will assess the clinical effectiveness of these treatments by examining their impact on patient outcomes such as survival, motor function, and quality of life.
The findings of this study will provide valuable insights to healthcare providers, policymakers, and patients, enabling them to make informed decisions regarding the allocation of healthcare resources for SMA type I treatment.

In the following chapter, the theory upon which this research is based will be explained, including the scope of the study and a summary of the conceptual framework. The third chapter will outline an overview of the research methods required for this analysis. The fourth chapter presents the results, while the final chapter will assess and discuss these results, comparing them to those of other studies. The research ends by proposing ideas for further investigation.

# 2. Theoretical framework

## 2.1 Background

The diagnosis of SMA involves a comprehensive assessment that combines clinical evaluation, genetic testing, and electromyography. The clinical evaluation entails thoroughly examining the medical history and physical indicators to identify motor symptoms and signs of muscle weakness[6,31]. Genetic testing is essential to detect SMN1 mutations, which confirm the diagnosis and determine the specific subtype of the disease[6,31]. The severity and type of SMA depend upon the number of SMN2 gene copies present. Infants affected by SMA type I typically exhibit clinical symptoms before six months of age and are unable to achieve independent sitting. Without medical intervention, individuals with this subtype generally do not survive beyond their second year of life[6]. Type II SMA manifests between 6 and 18 months of age, and while affected individuals may survive beyond the age of 20, they cannot walk and may achieve independent sitting. The onset of type III SMA occurs after 18 months, and individuals with this subtype can usually walk. The life expectancy of individuals with type III SMA is similar to that of the general population, although patients may experience progressive weakness and functional decline[6,7]. Type IV SMA, which begins in adulthood, typically follows a milder course[6,7]. This dissertation primarily focuses on the most severe subtype, SMA type I.

### 2.1.1 Treatment options SMA

In the Netherlands, individuals with SMA Type I have access to various treatment options, including medication, nutritional support, and gene therapy[21].

#### *Best supportive care*

The BSC for SMA Type I typically involves a multidisciplinary approach and includes respiratory and nutritional support, physical therapy, and psychological support for families. Respiratory therapy is a critical component of best supportive care for individuals with SMA Type I, as respiratory failure is the most common cause of death in these patients[2,32,33].

#### *Nusinersen*

Nusinersen works by increasing the production of the SMN protein. The treatment is administered via intrathecal injection and consists of four loading doses within two months and, after that, doses every four months[23,34].

Clinical trials showed that infants who received nusinersen presented improvements in motor function and muscle strength and a higher survival rate without the need for permanent ventilation compared to the placebo group[13,35]. Although nusinersen demonstrated effectiveness in treating SMA type I, it is accompanied by several drawbacks. One significant drawback is its administration method through intrathecal injection, which involves a lumbar puncture and may result in complications such as headache, nausea, vomiting, and back pain[36]. Furthermore, the high cost of nusinersen and the need for lifelong administration impose a financial burden on families and the healthcare system[33]. Results from cost-effectiveness studies of nusinersen treatment for SMA type I patients have been mixed[21,37–40].

#### *Onasemnogene abeparvovec*

OA is a gene therapy that carries a healthy copy of the survival SMN1 gene to motor neurons. This restores the production of the SMN protein, which is crucial for muscle function[16]. The effects of this treatment vary among patients, with certain individuals experiencing mild improvement while others demonstrate significant improvement, allowing them to sit and walk without support[16,41]. Since OA is administered through a single intravenous injection, it offers a significant advantage over nusinersen

by requiring only one dose throughout the treatment course. This characteristic reduces the burden on patients, providing a more convenient treatment option[20].

### *Nusinersen versus onasemnogene abeparvovec*

Based on a comparison of clinical trials between OA and nusinersen, the results of OA indicate better outcomes [13,15,18,19]. In the primary completed STR1VE-US study, it was observed that 20 out of 22 infants (91%) who underwent gene therapy (OA) remained alive and did not require permanent assisted ventilation (PAV) even after 14 months versus the results of the ENDEAR clinical trial utilizing nusinersen treatment that shows 49 out of 80 infants (61%) were still alive, after 18 months, and did not require PAV[15,19]. When considering various outcome measures such as survival, ventilation-free survival, and mobility in symptomatic SMA type I patients, OA appears to exhibit superiority over nusinersen. However, due to the indirect comparison, it is not possible to make conclusive statements about clinically significant differences between the two treatments[15]

## 2.1.2 New Born Screening Program

According to clinical experts, administering OA at an early stage, preferably prior to the appearance of symptoms, is expected to lead to improved outcomes[26]. Compelling evidence indicates that the progressive decline of motor neurons in patients diagnosed with SMA type I begins during the perinatal period. This results in severe denervation within the first three months and a loss of motor units before six months of age[26,42]. According to the summary of product characteristics, OA has the ability to save motor neurons that are still alive, but it cannot revive motor neurons that have already died[26].

Thus far, preclinical investigations involving severe SMA mouse models demonstrate that administering drugs at the earliest possible stage, before substantial motor weakness or loss, yields optimal outcomes[42].

Promising results of pre-symptomatic treatment have been published these last few years[30,35]. In clinical trials such as the SPR1NT study, the effectiveness, and safety of OA were evaluated in pre-symptomatic infants treated within six weeks of birth[30]. The final results for 14 infants with two copies of SMN2, expected to develop SMA type I, were compared to a similar natural-history cohort of 23 infants. The findings showed that all 14 infants could sit independently for at least 30 seconds before 18 months of age, with 11 achieving this milestone within the normal developmental timeframe. Additionally, all participants survived without permanent ventilation, and no treatment-related serious adverse events were reported. Published results from the NURTURE study, which investigates pre-symptomatic treatment with nusinersen, showed that all patients remained alive and did not require permanent ventilation[35]. These results demonstrate the safety and effectiveness of treatment in infants at risk of developing SMA type I and highlight the importance of implementing SMA in universal newborn screening (NBS) programs[30].

Furthermore, Jalali et al. (2020) found that universal NBS for SMA followed by treatment with nusinersen was cost-effective in the US. Also, a research study involving a team of 15 experts in SMA examined the impact of early diagnosis through NBS on infants with SMA. The findings revealed a remarkable opportunity to optimize the effectiveness of treatment by administering it before symptoms manifest. The experts strongly recommended immediate initiation of treatment for infants diagnosed with SMA through the NBS program in the United States[42,43].

These results support the deliberation that early identification and treatment of SMA type I is a more effective strategy and may be more cost-effective than treating patients after symptom onset [35,40,42,43].

On June 22, SMA was implemented into the NBS program of the Netherlands[44]. This decision was made following recommendations from the Health Council of the Netherlands in 2019[45]. The council expressed concerns about the potential minor health benefits of adding SMA to the NBS program and suggested that a (cost-effectiveness) evaluation in the future needs to determine whether NBS should be continued[45]. It is important to note that these recommendations were based on research involving nusinersen, as the advice was given in 2019 before the EMA approved OA[14,45] . The Netherlands is

among the first European countries to introduce NBS for SMA. Currently, only Norway, Germany, and the Wallonia region in Belgium also perform SMA screening for newborns. Other countries are conducting pilot projects for this purpose[46].

### 2.1.3 Cost-effectiveness literature

#### *Previous cost-effectiveness analysis OA*

Two cost-effectiveness analyses evaluated the use of OA compared to nusinersen and BSC for the treatment of SMA type I[21,22]. The study by Broekhoff et al. (2021) focused on the Netherlands and found that OA was cost-effective when compared to nusinersen and BSC[21]. However, the analysis also highlighted that the cost-effectiveness of OA was unlikely based on Dutch WTP reference values. The presence of uncertainty regarding the long-term effects of OA could impact the cost-effectiveness ratios[21].

On the other hand, Wang et al. (2022) conducted a cost-effectiveness analysis in Australia and determined that both nusinersen and OA provided health benefits for SMA type I patients[22]. However, neither treatments were considered cost-effective at the commonly used WTP threshold of $50,000 per quality-adjusted life-year (QALY). The study emphasized the need for high-quality clinical data and the exploration of appropriate WTP thresholds for rare diseases[22].

Overall, these analyses suggest that while OA may offer clinical benefits, its cost-effectiveness compared to existing treatments varies across different settings. The presence of uncertainties regarding its long-term effects and the establishment of suitable WTP thresholds are crucial considerations for decision-makers when determining reimbursement policies for (SMA type I) treatments.

#### *Conclusion HTA reports*

OA has been the subject of several cost-effectiveness analyses by various HTA agencies, including the Institute for Clinical and Economic Review (ICER), the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), and the Dutch National Health Care Institute (ZIN)[25–27,29]. This section will first discuss the ICER, NICE, and CADTH reports, and the subsequent paragraph will review into the ZIN report.

In summary, three HTA reports of ICER, NICE, and CADTH evaluated the cost-effectiveness of OA for the treatment of SMA type I. The ICER report concluded that the therapy is cost-effective, although it recognized the high cost and suggested alternative payment methods to improve access[27]. The NICE report acknowledged the effectiveness of OA but recommended its use within a managed access agreement due to its high cost[26]. Similarly, the CADTH report found that the therapy is also clinically effective, improving survival and motor function, but its cost-effectiveness exceeded the commonly accepted threshold [29]. Overall, the HTA reports recognized the clinical benefits of OA but raised concerns about its high cost and uncertainty about the long-term effectiveness. Further research and collaboration are needed to address uncertainties and inform reimbursement decisions.

#### *Cost-effective results OA Netherlands - ZIN*

In the Netherlands, the reimbursement policies for drugs are determined by the distinction between their usage within the hospital (referred to as “intramural”) or outside of the hospital (referred to as “extramural”). In the case of intramural drugs such as nusinersen and OA, reimbursement is based on an open and generic system. Under this system, if the disease indication is registered by the EMA and the “College ter Beoordeling van Geneesmiddelen” (CBG), and the drug is deemed to be at least as effective as the standard of care, it is automatically eligible for reimbursement without undergoing a cost-effectiveness assessment[47]. In the Netherlands, the Dutch Ministry of Health, Welfare, and Sport (VWS) has implemented a mechanism known as the “lock” for drugs with potentially high costs. This mechanism excludes such drugs from reimbursement until an evaluation is conducted to assess their effectiveness and cost-effectiveness[26,47]. OA underwent this evaluation process in 2021. The ZIN report

of 2021 evaluated the clinical and cost-effectiveness of OA for treating SMA type I patients in the Netherlands[28]. OA was determined to be more cost-effective compared to nusinersen or BSC. However, the estimated ICER of €241,798 per QALY gained (when comparing OA to BSC) was above the cost-effectiveness threshold typically used in the Netherlands for orphan drugs (€80,000 per QALY). However, ZIN also noted that the ICER was sensitive to several variables, including the drug price, the time horizon of the analysis, and the assumptions regarding the effectiveness and safety of the therapy[28].
Based on the available evidence, ZIN concluded that OA is effective in treating SMA type I patients and has a positive effect on the quality of life. However, the treatment costs are high, and there are still uncertainties regarding its long-term effectiveness and safety. Therefore, ZIN recommended that OA should only be reimbursed for patients who meet specific criteria, such as being diagnosed with SMA type I before six months of age and having no other treatment options available. Additionally, ZIN suggested further research to address the remaining uncertainties, such as the long-term effectiveness and safety of the treatment[28].

These studies provided evidence suggesting that OA is likely to be a more (cost-)effective treatment option when compared to BSC. Nevertheless, the calculated ICER exceeds the WTP threshold due to the high costs of the treatment, and there remains limited evidence regarding its long-term effectiveness. With the availability of newly published clinical trial data from the STR1VE-EU and SPR1NT trials, it becomes possible to reevaluate the cost-effectiveness of OA compared to BSC.

## 2.2 Conceptual framework

### 2.2.1 Economic evaluation

Economic evaluation is a crucial tool in determining the value of different interventions, policies, or programs. Several types of economic evaluations are used to measure the impact of these interventions, including cost-effectiveness analysis, cost-benefit analysis, and cost-utility analysis[48].
In a cost-effectiveness analysis, the incremental costs of each intervention are compared against the incremental health outcomes, usually measured in terms of clinical outcomes such as life years (LY) gained or symptom improvement. This type of analysis is often used to determine which intervention provides the best value for money. In a cost-utility analysis, the health outcomes are measured using QALYs. QALYs combine both the quantity and quality of life gained from a particular intervention, with one QALY being equivalent to one year in perfect health. This approach allows for a more nuanced understanding of the impact of an intervention on health outcomes[48].
Both cost-effectiveness and cost-utility analyses are important tools for decision-makers in healthcare and other fields to allocate resources efficiently and effectively. Following the guidelines for economic evaluation in the Netherlands, this study will measure and present health outcomes in terms of both LY and QALYs gained[49].

### 2.2.2 Decision-analytic modeling

It is recommended to conduct an economic evaluation alongside a clinical study, where all relevant costs and effects for the patient population are measured within a single randomized controlled trial (RCT). However, since such data is not available for this particular research, an alternative approach is to utilize decision-analytic modeling[50]. This type of modeling enables the accumulation and utilization of data from multiple sources in a single model, allowing for the measurement and comparison of costs and consequences of treatments beyond the available observed data[48,50]. In order to select an appropriate decision-analytic model for this research, it was essential to establish the link between the specific aspects of the disease and treatment regimens and the different assumptions of the model. The objective of the OA treatment is to gain motor skills (independent sitting and walking) and overall survival (OS) of patients with SMA type I[18,19,30]. Hence, five distinct health states were identified: 'not sitting and PAV free', 'PAV', 'sitting independently', 'walking independently', and death. These health

states are mutually exclusive and collectively exhaustive, meaning that individuals can only be in one of these states at any given time[48]. It was not possible to go back to a health state, and the death state is absorbing, implying that once an individual reached the death state, they were not able to transition to any other state. Furthermore, based on findings from the STR1VE-US/EU and SPR1NT trials, it was evident that the probability of transitioning between health states (e.g., gaining motor skills, PAV) varies over time[18,19,30]. Incorporating the assumptions of mutually exclusive and collectively exhaustive health states along with time dependency, a Markov model was employed as a decision-analytic model[48].

A Markov model was used to assess the probability of a patient being in each health state over discrete time periods known as cycles[48]. Each health state was associated with a specific cost and utility value. To calculate the expected costs and outcomes, the relevant cost and utility values associated with the health state and the time during which the average patient remains in a health state are used[48]. Estimating the number of patients in each health state after each cycle can be accomplished by assigning probabilities to various transitions within the model. The transition probabilities are derived from published literature[51].

### 2.2.3 Survival analysis

For the BSC arm, survival data from natural history studies were presented as non-parametric Kalpan-Meier (KM) survival curves. For the OA treatment arm, patient-level data from published literature was available that consists of information on patients when they transition into a specific health state. The data available for the different treatment arms were until the end of the study period. However, for the purpose of this study, it is crucial to determine the long-term survival outcomes of the population, extending beyond the observed time period. This was accomplished by extrapolating the KM survival curves and patient-level data estimates using either semi-parametric or parametric extrapolation techniques[52]. The parametric distributions considered in this study include the exponential, Weibull, Gompertz, log-normal, and log-logistic distributions. All of these parametric distributions have been modeled and tested in the analysis, and the most suitable distribution was determined in accordance with the NICE guideline on survival analysis[52].

Statistical tests can be applied to evaluate and compare different parametric models, supporting to select the most appropriate one. The Akaike information criterion (AIC) and the Bayesian information criterion (BIC) are two commonly used statistical tests for this purpose. These tests are designed to identify the parametric survival model that minimizes the loss of information resulting from the modeling process[52]. In addition to these tests, assessing the goodness of fit between a parametric survival model and clinical data can be done by visually examining how closely the model aligns with the KM survival curve. However, it is important to note that the presence of censoring, where the time-to-event data is incomplete, introduces uncertainty and may affect the accuracy of this method[52].

### 2.2.4 Uncertainty

In order to ensure a robust and unbiased response to the research question, it is crucial to acknowledge the presence of uncertainty regarding the results of the model[49]. Various forms of uncertainty exist, and it is important to distinguish between variability, heterogeneity, and uncertainty. Variability refers to the phenomenon where patients with similar baseline characteristics and probabilities may encounter varying outcomes due to chance[50]. Heterogeneity, on the other hand, relates to dissimilarities among patients that can be explained, to some extent, by variances in baseline characteristics[50].

The objective of using a Markov model is to capture uncertainty rather than variability and heterogeneity. There are two types of uncertainty: parameter uncertainty and structural uncertainty. This study will evaluate parameter uncertainty through deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA)[48,50]. DSA involves altering individual parameter assumptions to

test their impact on the ICER, while a PSA involves simultaneously analyzing multiple parameters, resulting in the calculation of multiple 'new' ICERs. The outcomes of the PSA will be presented in a cost-effectiveness plane (CE-plane), and a cost-effectiveness acceptability curve (CEAC) can be generated from the PSA findings. The CEAC shows the probability of each treatment being cost-effective based on different WTP thresholds[50]. Structural uncertainty, however, is not related to parameters but to the assumptions imposed by the modeling framework. Scenario analysis can be used to evaluate structural uncertainty[48,50].

### 2.2.5 Cost-effectiveness decision

Based on the incremental cost and effects of OA treatment compared to BSC, it is possible to compute an ICER and an incremental net monetary benefit (NMB). The ICER assesses the incremental costs per LY and QALY gained. At the same time, the NMB transforms the incremental effect of the new treatment into monetary value using the WTP as the measure of each unit of effect[50]. A positive NMB indicates that the intervention is cost-effective relative to the comparator.

The WTP in the Netherlands varies between €10,000 and €80,000 per QALY gained and depends upon the disease burden and incidence of the disease[53,54]. Since SMA (type I) is a rare disease (incidence <5 per 10,000 inhabitants of the EU), treatment for SMA has been granted the status of 'orphan drug'. This implies, along with the high disease burden, that the WTP threshold for new medications for this disease is higher compared to other medications. The WTP threshold for SMA type I is €80,000[28]. If the ICER falls below this threshold, the intervention is likely to be cost-effective. Conversely, a significantly higher ICER value suggests that the costs associated with the new treatment are too high, the treatment's effect size is insufficient, or a combination of both factors[53,54].

# 3. Research Methods

## 3.1 Outlining

### 3.1.1 Perspective – general

This research follows Dutch guidelines for economic evaluations using a societal perspective, which includes all relevant societal costs and benefits, regardless of who bears the costs or receives the benefits[49].

### 3.1.2 Target Population

The target population in this analysis simulates a patient population with a clinical diagnosis of SMA Type I, a bi-allelic mutation in the SMN1 gene, and up to two copies of the SMN2 gene. The scenario analysis will evaluate a patient population of pre-symptomatic infants with two copies of SMN2 at risk for SMA type I. This is the same population as was used in the ZIN report[28].
Patients who were symptomatic and diagnosed with type I SMA and treated before six months of age were included in the STR1VE-US and STR1VE-EU clinical trials[18,19]. Their outcomes served as the basis for the model population. In the SPR1NT trial, pre-symptomatic children treated ≤6 weeks of life were used as the basis of the scenario analysis[30].

### 3.1.3 Treatment structure

For the cost-effectiveness analysis, OA is the intervention treatment, and BSC is the comparator treatment. OA is a single-dose intravenous gene therapy designed for the early stages of a patient's life. The standard of care for patients in the Netherlands with SMA type I involves comprehensive support with ventilatory, gastrointestinal, and nutritional support, as well as physiotherapy delivered via a multidisciplinary team[55,56].

### 3.1.4 Health outcomes

Prognosis of infants with SMA type I is poor. Without treatment, patients usually die before two years of age and will not acquire any motor milestones (e.g., sitting and/or walking independently)[7,8]. The WHO motor milestones encompass a collection of six key milestones that are universally recognized as essential for the development of independent walking[57]. This research takes into account various health outcomes, including OS and acquiring PAV. Additionally, the study considers two important motor milestones: independent sitting (> 30 seconds) and independent walking, as additional health outcome measures. Data was collected from published RCTs and natural history trials for these health outcomes[18,19,30,58–60].

### 3.1.5 Model outcomes

Both costs and LY are accumulated in order to estimate the total costs and clinical outcomes of each treatment. Costs were calculated per cycle for each respective health state. This approach enables to calculate the (incremental) expected costs, (incremental) LY, and (incremental) QALYs for each group, and eventually, the ICER could be calculated. By comparing the ICERs, the difference between the treatment OA and BSC can be determined.

The ICER was obtained by dividing the difference in costs between treatment and comparator by the difference in QALYs. This ratio reflects the cost per QALY gained, which is the primary outcome of interest in this study for the indirect comparison between the two groups. Moreover, the cost per LY gained will also be reported. The maximum WTP threshold for orphan drugs in the Netherlands is €80.000 per QALY gained[53]. Therefore, recommendations about the cost-effectiveness of the treatment will be made based on this threshold value.

### 3.1.6 Time horizon

The model utilized a lifetime horizon of 99 years, with monthly cycles, in order to accurately capture transitions between health states. Specifically, since patients in health states 'not sitting van PAV free' and 'PAV' have an average survival of up to 2 years, monthly cycles were deemed necessary to provide sufficient detail for survival modelling[7]. In addition, the monthly cycle length was also necessary to deliver appropriate information for the relatively short timeframe within which infants transition to independent sitting and walking[57]. Lastly, the use of a lifetime horizon was essential, as survival rates for individuals with SMA type III are comparable to those of the general population, which are used as a proxy for treated patients with SMA type I who can walk independently[6,61].

### 3.1.7 Discount rates

The Dutch National Health Care Institute's guidelines for HTA recommend annual discount rates of 4% for costs and 1.5% for utilities[49]. Thus, in compliance with these guidelines, the costs of the intervention will be discounted at a yearly rate of 4%, while the utilities will be discounted at an annual rate of 1.5%[49]. A half-cycle correction is applied to both costs and effects to overcome the Markovian assumption [51]. Markov models assume that transitions occur between different time intervals or cycles and that the patients remain in each state of the model throughout the entire cycle. However, in reality, patients move between different phases of their disease continuously rather than at specific points in time. Instead of assuming that patients transition between states only at the beginning or end of a cycle, a method called half-cycle correction is used to address this issue. The half-cycle correction accounts for the continuous movement of patients and provides a more accurate representation of their transitions between states[51].

## 3.2 Model structure

Due to the nature of the disease and the fast prognosis, patients could experience changes in their health states. Because patients could experience multiple health states, a Markov model is used. A Markov model consisting of five health states (not sitting and PAV free, PAV, sitting independently, walking independently, and dead) will be replicated to simulate the life course of patients diagnosed with SMA type I. Markov models are commonly used in healthcare interventions' economic evaluations, where they follow a group of patients over time as they transition between different health states, including death[48,62].

The submitted model is replicated using information from published economic evaluations for treating SMA Type I patients[21–23,26–29]. The model focuses on three main factors of the disease; gaining functional motor milestones, the need for PAV, and survival or time to death. The achievement of functional motor milestones and survival are correlated and is generally improved with treatment. Figure 1 shows the model structure, simulating the possible life courses of patients diagnosed with SMA type I. The model includes four health states and one absorbing 'dead' state. Each state is associated with different utilities and costs, reflecting the severity of the disease.

The model begins with patients entering the 'not sitting and PAV free' health state as infants. In the subsequent cycle, patients can either improve and transition to the 'sitting independently' state or experience worsening and move to the 'PAV' state or die. If patients achieve the motor milestone of 'sitting independently', they can progress to the 'walking independently' state in the next cycle. Except for the 'dead' absorbing health state, patients in other health states can either stay in their current state or die in the next cycle.

The model consists of two phases: the first stage is a short-term model of 36 months that uses data from clinical trials. The second stage is a long-term model that lasts up to 99 years. The model is based on assumptions and extrapolations of survival and acquiring functional motor milestones data. It is assumed that the motor milestones achieved before 36 months (end of short-term model) sustain until death since no information is known on the long-term effectiveness of OA. Regression from higher health states to worse health states is not possible. Monthly cycle lengths are chosen, which are appropriate given the changes in childhood development at a young age[57].

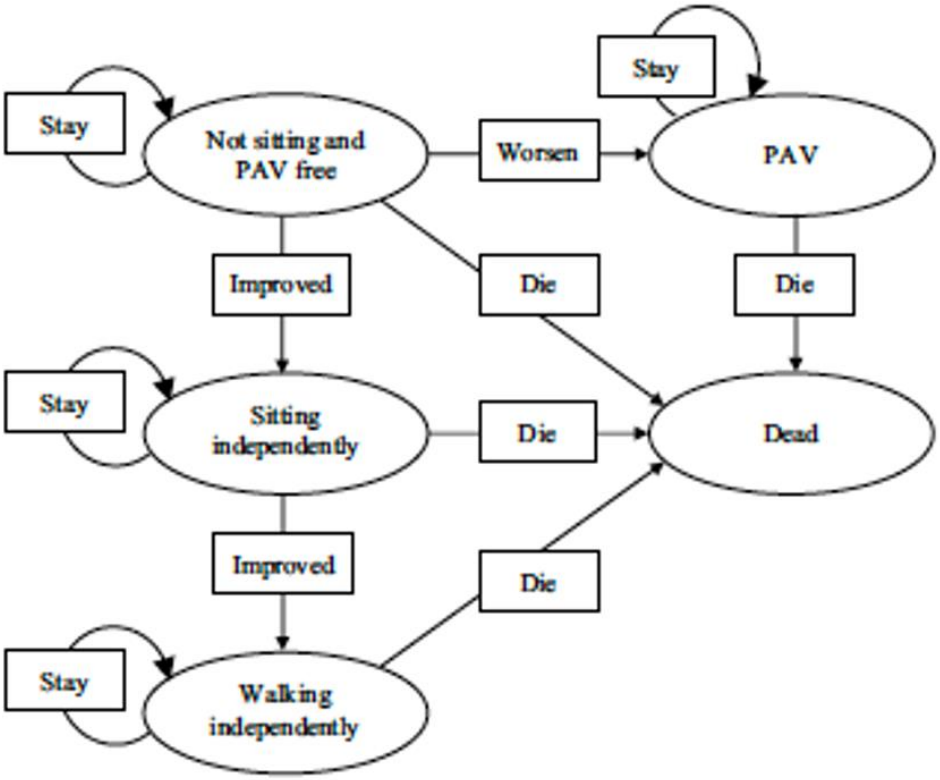



*Figure 1: Structure of Markov model of SMA type I[22].*

## 3.3 Model inputs

The data inputs for cost and effects are identified, measured, and valued according to the economic evaluation guidelines in the Netherlands[49]. Economic and statistical analyses are carried out using Microsoft Excel 2023 and Rstudio.

### 3.3.1 Data sources

Given the ethical considerations related to the inclusion of placebo arms in clinical trials for treating SMA type I patients[18,19], there is currently a lack of direct comparative trials between OA and BSC or nusinersen. Additionally, since there were no other available treatments for SMA type I patients at the time of the OA studies, non-comparative studies or indirect treatment comparisons are the most viable and suitable approaches for evaluating the efficacy of OA. Table 1 provides a comprehensive overview of the different data sources used to assess the health state transitions and treatment arms.

| Health state transition | BSC | OA treatment |
|---|---|---|
| All patients start in 'not sitting and PAV free' state | | |
| not sitting and PAV free → sitting<br>sitting → walking | Not possible for BSC | Pooled data from STR1VE-US and STR1VE-EU (n=42) |
| not sitting and PAV free → PAV<br>not sitting and PAV free → dead | NeuroNEXT (n=16) | Pooled data from NeuroNEXT and STR1VE (n=58) |
| sitting → PAV<br>walking → PAV | - | Assumed not possible in the model |
| sitting → dead | - | SMA type II patients Zerres et al. 1997 (n=240) |
| walking → dead | - | National life tables CBS |
| PAV → dead | Gregoretti et al. 2013 (n=24 patients receiving non-invasive ventilation only, not tracheostomy) | |

*Table 1: Data sources used for health state transitions*[18,19,58–60].

### *OA clinical trial data*

The STR1VE-US trial, conducted in the US, was a phase III trial that followed an open-label, single-arm, single-dose design. It took place at 12 hospitals and universities, enrolling a total of 22 eligible patients. Inclusion criteria required patients to be under six months of age and have SMA type I with biallelic SMN1 mutations (deletion or point mutations) and one or two copies of SMN2[19].

Similarly, the STR1VE-EU trial was a multicenter phase III trial carried out at nine sites across Italy, the UK, Belgium, and France. It employed an open-label, single-arm, single-dose design with similar inclusion criteria as the STR1VE-US trial, enrolling 33 patients. Among the 33 patients who completed the study and were included in the STR1VE-EU trial, 13 initially required ventilatory and/or feeding support at baseline. Therefore, these patients were excluded from the analysis to ensure better comparability of baseline characteristics between the two trials and enhance the validity of the conclusions[18]. Unfortunately, due to data confidentiality reasons, it was not possible to incorporate the START trial with its extended follow-up period into our analysis[16,17,63].

### *Data sources per health state transition*

The subsequent sections will provide a description of the data sources associated with each health state transition.

#### not sitting and PAV free → sitting → walking

As previously stated, published patient-level data from the STR1VE-US and EU trials are extracted from the papers and utilized for the OA treatment arm. This data serves as the basis for the transitions from the 'not sitting and PAV free' state to the 'sitting' state and from the 'sitting' state to the 'walking' state[18,19].

#### not sitting and PAV free → PAV → dead

Data for the transition from the 'not sitting and PAV free' state to 'PAV' and 'dead' in the BSC arm are obtained from a published paper regarding a prospective natural history study, namely the NeuroNEXT trial, which enrolled SMA infants. The analysis focused on patient-level data from 16 SMA type I patients with two copies of the SMN2 gene. This study's inclusion criteria and time frame aimed to replicate the expected criteria and time frame used in future clinical trials with SMA treatment in infants[60].

For the OA treatment arm, pooled data from the NeuroNEXT trial and STR1VE-US/EU trials from the published papers are used. This resulted in a sample size of 58 infants[18,19,60].

#### sitting/walking → dead

To estimate the transition from 'sitting' to 'dead' and 'walking' to 'dead', a methodology similar to that employed in the ZIN report is used[28]. The ZIN report assumes that patients with SMA type II serve as proxies for treated patients with SMA type I in the 'sitting' health state, while patients with SMA type III serve as proxies for treated SMA type I patients in the 'walking' health state. The data for SMA type II patients is obtained from a published study by Zerres et al. (1997)[59].
Based on the understanding that individuals with SMA type III typically have an average life expectancy. It is assumed that individuals in the 'walking' health state have a life expectancy equivalent to that of the general population. Therefore national life tables are used for the transition from 'walking' to 'dead'[61].

#### PAV → dead

The transition from the 'PAV' state to 'dead' across both arms is determined using OS data obtained from a published paper by Gregoretti et al. (2013), where a retrospective chart review was performed of SMA type I patients. Patients receiving non-invasive ventilation are used. Data pertaining patients with a tracheostomy are excluded from the analysis, as clinical experts have indicated that this procedure is not commonly employed for such patients[28,58].

### 3.3.2 Clinical effectiveness data

To fill the Markov traces, two types of data were available; published patient-level data and Kaplan Meier survival data.

#### *Patient-level data*

Published papers with STR1VE-US/EU and NeuroNEXT trial results consisted of patient-level data[18,19,60]. The published papers regarding the STR1VE-US/EU trials provided detailed information on the age of patients when specific motor milestones were achieved, as well as the age at the cutoff or final visit. In the case of the published research regarding the NeuroNEXT trial, data extraction is performed using the WebPlotDigitizer tool[64].

#### *Kaplan Meier survival data*

The study from Zerres et al. (1997) and Greoretti et al. (2013) contained survival curves[58,59]. To obtain the OS data from the non-parametric KM curve, WebPlotDigitizer and the method proposed by Hoyle and Henley is used[64,65].

### 3.3.3 Extrapolation of survival data

In order to make predictions or estimate outcomes for time periods beyond the observed data, it is necessary to extend the analysis by fitting a survival distribution. This extrapolation process enables the projection of survival probabilities or event rates into the future or into intervals that have not been directly observed[48]. Assuming that the observed patterns will continue to hold beyond the available data, the fitted survival distribution can be used to model the patterns and trends observed in the existing data. This approach becomes particularly valuable when dealing with a limited duration of observed data or when the primary interest lies in long-term outcomes[48].

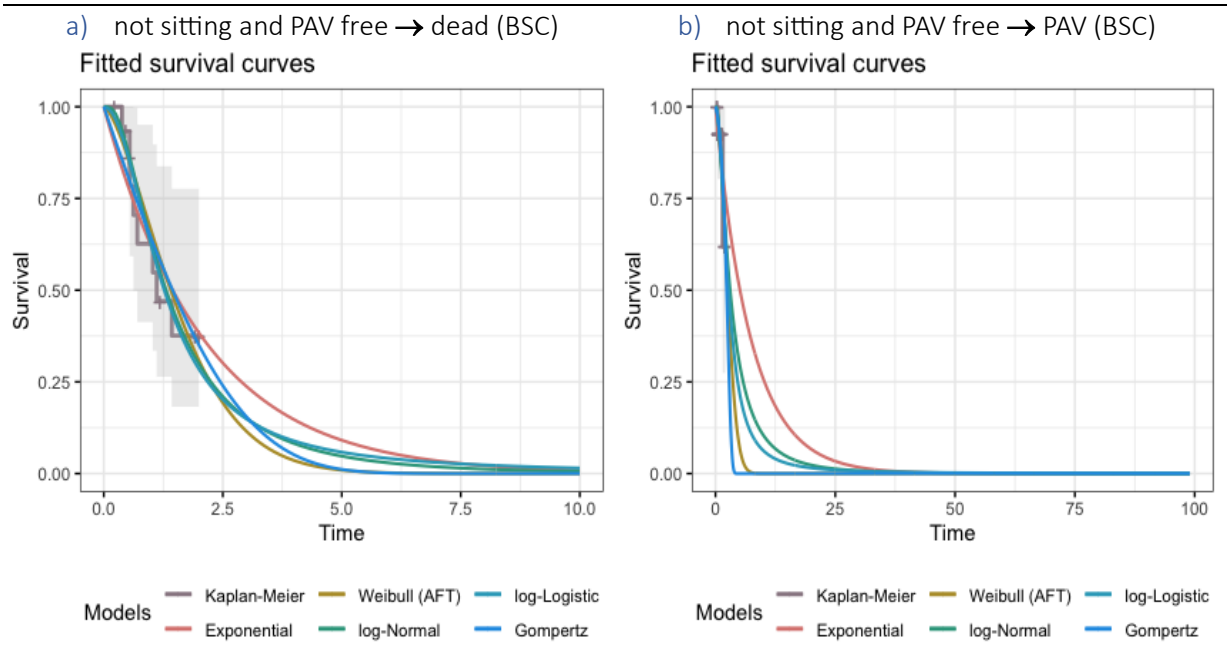
Given the focus on long-term outcomes and the availability of only limited follow-up data, extrapolation is required in this study. The survival analysis and survival data are described by extracting the outcomes of 'not sitting and PAV free', 'sitting', 'walking', 'PAV', and 'dead' transitions. Since the data consisted of a single arm (group) only, Rstudio is used to fit parameter distributions based on the extracted

patient-level data and KM curves. Age differences are used to establish the parameter outcomes. The subsequent paragraph will provide an explanation of the process employed to determine the choice of parametric distribution.

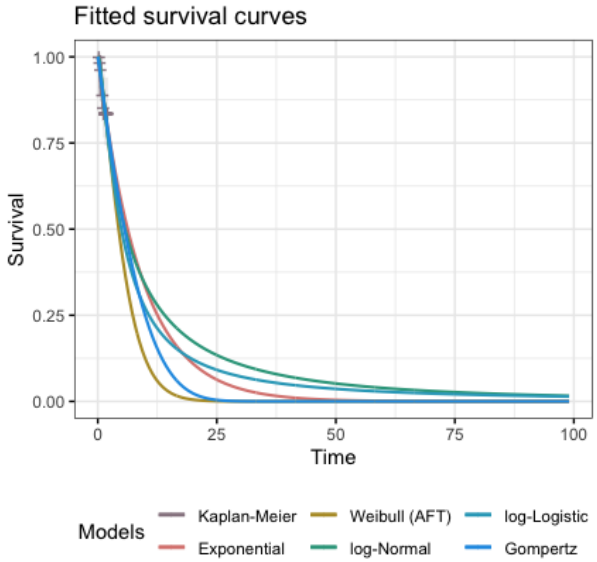
### *AIC and BIC tests & Visual inspection*

Various parametric models are examined to identify the most appropriate distribution (i.e., Weibull, log-logistic, Exponential, log-normal, and Gompertz). In the appendix (Appendix 1 – AIC and BIC overview), the AIC and BIC values of the models are shown based on the KM data and published patient-level data from the trials. The highlighted portion of the tables indicates the parametric models found to be the most suitable for each transition stage in the different treatment arms (BSC, OA, and BSC & OA), as determined by the AIC and BIC statistical tests.

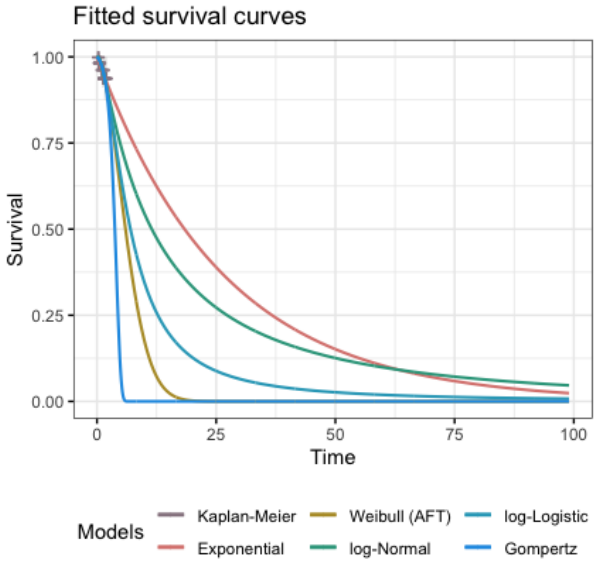
Figure 2 shows the extrapolated distributions of the different transitions of the OA and the BSC treatment arms. The time horizon of the figures is set to 10 or 99 years, to provide enough evidence to visually inspect differences in survival distributions between the different models. The time horizon for the transition to sitting and walking independently is set to 3 years (36 months). The disparities among the parametric distributions become evident when examining their long-term survival predictions, which can be visually observed by examining the tails of the distributions. Generally, the log-normal and log-logistic distributions exhibit significantly heavier tails than the Weibull, Gompertz, and exponential distributions. This is because the former distributions assume a diminished risk of an event occurring after a specific point in time.



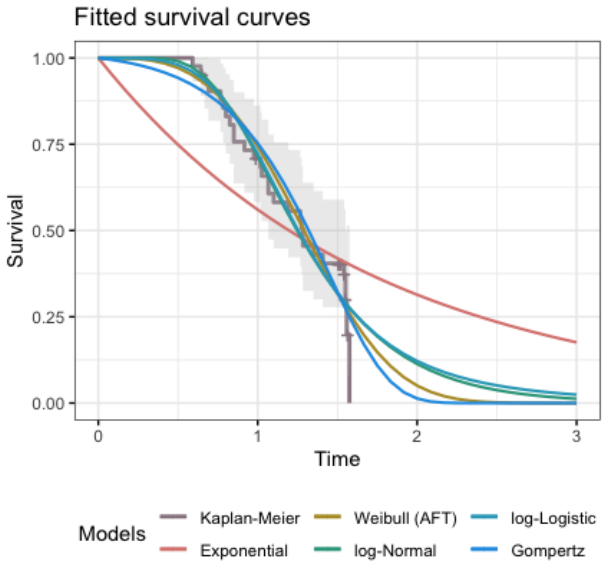
c) not sitting and PAV free → dead (OA)



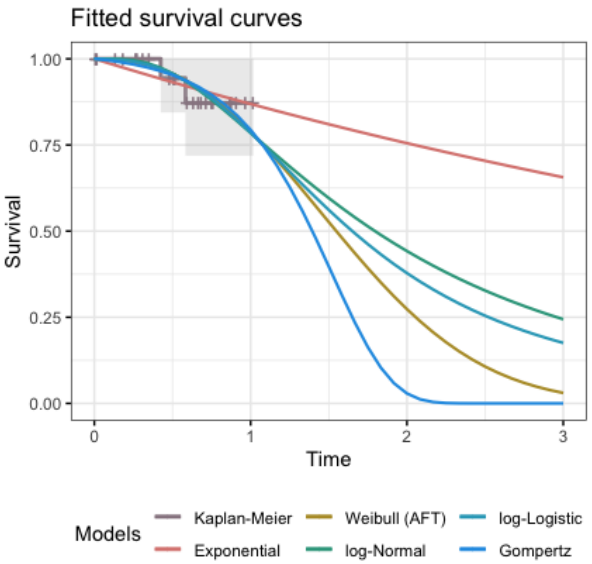

d) not sitting and PAV free → PAV (OA)




e) not sitting and PAV free → sitting




f) sitting → walking



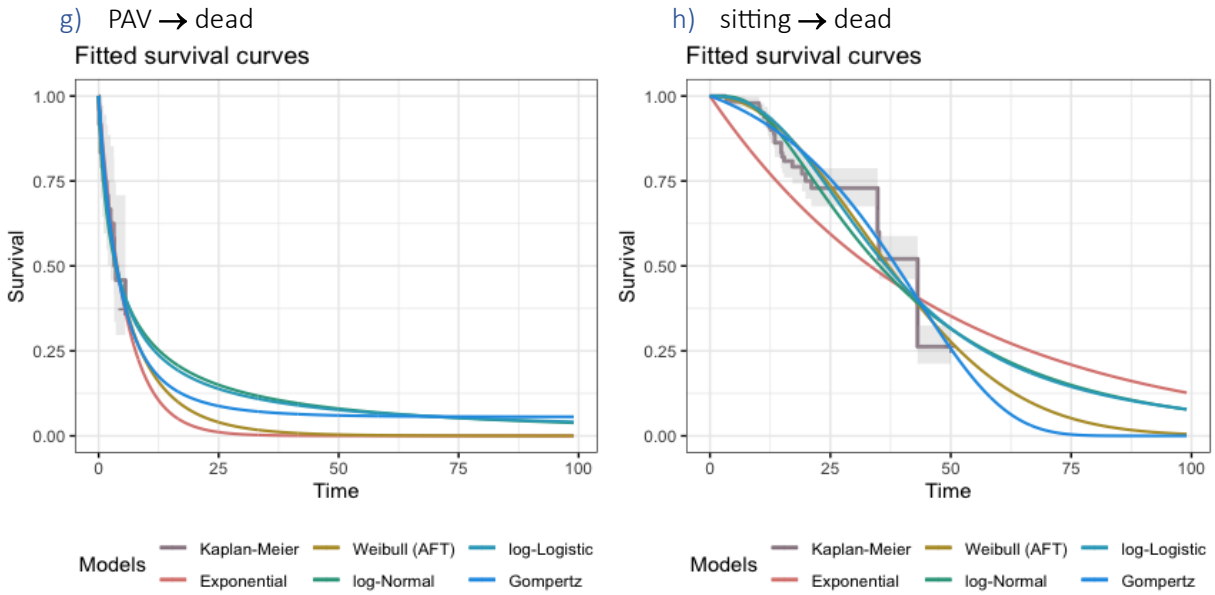



*Figure 2abcdefgh: Extrapolation of the health state transitions.*

### *Choice of distributions*

The forthcoming section presents a detailed explanation for selecting a distribution per transition based on the AIC & BIC tests and visual inspection. An overview of the chosen distributions is shown in Table 2.

### not sitting and PAV free → dead

The transition from 'not sitting and PAV free' to 'dead' is modeled using a log-normal distribution for both treatment arms. This choice is based on statistical tests that indicated the log-normal distribution had the lowest AIC and BIC values, and the shape of the curve aligned logically with the data.

### not sitting and PAV free → PAV

For the transition from 'not sitting and PAV free' to 'PAV', significant differences are observed in the graphs, particularly in the OA treatment arm. An exponential distribution seems the best fit for this transition in both treatment arms. The decision is based on the lowest AIC and BIC values and visually inspecting the distribution curves.

### not sitting and PAV free → sitting

When examining the transition from 'not sitting and PAV free' to 'sitting', the distributions exhibited similar patterns except for the exponential distribution. Based on the results of goodness-of-fit tests, a log-normal distribution is selected due to its lowest AIC and BIC values.

### sitting → walking

Regarding the transition from 'sitting' to 'walking', the log-normal distribution had the lowest AIC value. However, a log-normal distribution seemed inappropriate because only a small proportion of patients reached the walking stage by the end of the clinical trial (Figure 2f). Instead, an exponential distribution seemed the best fit as it better aligned with the observed results and had the lowest BIC value. The AIC value of the exponential distribution was the second lowest after the log-normal distribution.

### PAV → dead

The exponential distribution is selected as the best fit for the transition from 'PAV' to 'dead'. The Gompertz, log-logistic, and log-normal distributions indicated survival beyond 99 years, which seemed inappropriate given the estimated survival time. The exponential and Weibull distributions showed a better fit. Since the exponential distribution had the lowest AIC and BIC values, it was deemed the most suitable choice.

### sitting → dead

Lastly, for the transition from 'sitting' to 'dead', data was available up to 50 years, reducing uncertainty in the extrapolation. The distributions exhibited similar courses, but the Gompertz distribution seemed the best fit based on its lowest AIC and BIC values. This choice aligned with the understanding that patients with SMA who achieve the sitting milestone are unlikely to survive beyond 75 years.

| Health state transition | BSC | OA treatment |
|---|---|---|
| not sitting and PAV free → sitting | - | Log-normal |
| sitting → walking | - | Exponential |
| not sitting and PAV free → PAV | Exponential | Exponential |
| not sitting and PAV free → dead | Log-normal | Log-normal |
| sitting → dead | - | Gompertz |
| walking → dead | - | National life tables[61] |
| PAV → dead | Exponential | |

*Table 2: Overview of the chosen survival distributions of each treatment arm in this model.*

### 3.3.4 Health state utilities

Assigning utility values to each health state in the model presents challenges, especially when dealing with infants and toddlers affected by a rare disease. Notably, the clinical trials of OA lacked a method to capture health-related changes in quality of life[18,19,58–60]. Multiple reports and cost-effectiveness studies, including NICE, ICER, ZIN, and CADTH, exhibited considerable variation in utility weights (Table 3)[26–29]. None of the studies seemed to fully represent the impact of illness on all health states.

| Health states | ICER[27] | NICE[26] | CADTH[29] | ZIN OA[28] | ZIN nusinersen[39] | Broekhoff et al.[21] | Wang et al.[22] |
|---|---|---|---|---|---|---|---|
| **PAV** | 0.190 | 0.00 | 0/0.19 | 0.00 | 0.733 | 0.733 | 0.104 |
| **not sitting and PAV free** | 0.190 | 0.190 | 0.190 | 0.19 | 0.733 | 0.733 | 0.104 |
| **sitting independently** | 0.600 | 0.600 | 0.600 | 0.60 | 0.752 | 0.752 | 0.115 |
| **walking independently** | Gen pop. | General pop. | General pop. | General pop. | 0.878 | 0.878 | 0.252 |

*Table 3: Comparison of utility values used in the existing literature for patients with SMA.*

Table 3 provides an overview of the utility values used in various studies. Notably, the Dutch cost-effectiveness analysis and the ZIN report of nusinersen employed remarkably high utility values, which may be considered disproportionate given the disease burden[21,39]. In contrast, the cost-effectiveness analysis conducted in Australia adopted more conservative values[22].

Generally, the utility values across the HTA reports were relatively similar[26–29]. For the health states 'not sitting and PAV free' and 'sitting independently', consistent utility values were employed, leading us to adopt similar values of 0.190 and 0.600, respectively (Table 4).
However, there is variation in the utility values for the 'PAV' state, with some studies using 0 and others using 0.19 as the utility value. The ZIN report of OA lacked a clear rationale for the selected utilities, and concerns were raised regarding the extreme assumptions[28]. Specifically, a clinical perspective highlighted the necessity of distinguishing utility values between 'PAV' and 'not sitting and PAV free' states since an infant free from PAV should have a different utility than an infant in the 'PAV' state[27]. Given the lack of reasonable values for the 'PAV' health state, the average of both approaches was calculated, resulting in a utility value of 0.095 for the 'PAV' state.
When considering the utility values associated with walking independently, the reports have used utility values derived from the general population[26–29]. However, concerns have been raised regarding the appropriateness of this comparison, as individuals with SMA who can walk may still have lower utility values compared to healthy individuals. To address this, a more conservative approach was followed by selecting a utility value of 0.85 for walking independently. This choice was based on the ZIN report of nusinersen and the comments provided in the ZIN report of OA, which indicated that this value would be more suitable in capturing the utility of walking independently for SMA patients[28,39].

| | |
|---|---|
| PAV | 0.095 |
| not sitting and PAV free | 0.190 |
| sitting independently | 0.600 |
| walking independently | 0.850 |

*Table 4: Utility values used in this research.*

### 3.3.5 Costs input and resource use

From a societal perspective, direct costs, both within and outside of healthcare, should be included in the analysis. This model includes direct medical costs, direct non-medical costs, and indirect non-medical costs. The costs associated with the different health states vary and are shown in Table 5.

Within the model, the healthcare costs associated with SMA type II and SMA type III patients receiving BSC are used as approximations for SMA type I patients receiving OA treatment. It is assumed that patients in the 'sitting independently' health state would have healthcare costs comparable to those of SMA type II patients receiving BSC. In contrast, patients in the 'walking independently' health state would have healthcare costs similar to SMA type III patients receiving BSC. This methodology is adopted from the ZIN and ICER reports [27,28].

An important source for determining the costs per patient per year is the cost-of-illness study conducted by Klug et al. in Germany in 2016[28,66]. This study provided valuable insights into the average medical and non-medical expenditures associated with each subtype of SMA. All expenses are classified into different categories of costs and expressed in euros, with currency conversion to Dutch price levels based on German vs. Dutch purchasing power parity (PPP). Furthermore, adjustments are made to account for the price level changes up to 2022[67].

Similarly, with utility values, there is a lot of uncertainty containing the cost of SMA. This study adopts the cost calculations used in the ZIN report of nusinersen, which are also examined in the scenario analysis of the ZIN report of OA. In the discussion section, the costs are reviewed in detail.

#### *Direct medical costs*

Direct medical costs are all expenses directly related to the prevention, diagnosis, therapy, rehabilitation, and care of the disease or treatment.

Treatment with OA is administered via a one-time intravenous infusion. A provisional price of €2.195.905 is used since there is no available information on the cost of OA in the Netherlands. This price is based on the ZIN report[28]. Administration costs of OA are €3.701, which include day-care costs for administration (€2.453) and one-hour infusion costs (€1.248). An overview of other direct medical costs is provided in Table 5. The direct medical costs are divided into four categories: respiratory care, gastrointestinal care, nutritional care, and orthopedic care.

*Direct non-medical costs*

Direct non-medical costs are expenses that occur outside of the healthcare sector. However, these costs are still directly related to the disease or treatment. In this model, transport costs and informal care costs are included as direct non-medical costs.

*Indirect non-medical costs*

Indirect non-medical costs refer to expenses that arise from having SMA (type I) outside of the healthcare system, such as the costs related to decreased productivity due to the condition and other out-of-pocket costs.

| Health state costs (€ per year): | PAV/not sitting and PAV free (SMA Type I) | sitting independently (SMA Type II) | walking independently (SMA Type III) |
|---|---|---|---|
| **Medical costs (€ per year):** | | | |
| Respiratory care | € 57,724 | € 12,095 | € 6,023 |
| Gastrointestinal care | € 4,930 | € 1,986 | € 1,484 |
| Nutritional care | € 4,589 | € 1,853 | € 1,353 |
| Orthopedic care | € 5,834 | € 4,819 | € 3,458 |
| Total costs | € 73,076 | € 20,753 | € 12,317 |
| **Monthly 2022€** | **€ 6,090** | **€ 1,729** | **€ 1,026** |
| **Non-medical (€ per year):** | | | |
| Transport | € 2,789 | € 2,751 | € 4,617 |
| Informal care | € 42,534 | € 38,527 | € 17,398 |
| Other out of pocket | € 16,813 | € 39,182 | € 15,035 |
| Lost productivity | € 18,823 | € 48,613 | € 33,848 |
| Total costs | € 80,959 | € 129,073 | € 70,897 |
| Monthly 2022€ | **€ 6,747** | **€ 10,756** | **€ 5,908** |
| **Price of intervention one-time costs** | | | |
| Drug acquisition costs OA | **€ 2,195,905** | | |
| Drugs administration costs | **€ 3,701** | | |

*Table 5: Costs overview in 2022€.*

## 3.4 Uncertainty

### 3.4.1 Deterministic sensitivity analysis – one-way sensitivity analysis

The DSA involves modifying single-parameter assumptions to assess their influence on the ICER. The results of the DSA are visualized in a tornado diagram, as presented in the results chapter (4.2.2). Table 6 and Table 7 below provide an overview of the parameters examined in the DSA. An absolute value change of 0.1 is used for both the upper and lower limit of the utility parameters, while the cost parameters are modified by 20%. The range of changes for the discount rates is established with zero

as the lower limit and a doubling of the base-case value as the upper limit. These alterations are based on the HTA's published by NICE, ICER, CADTH, and ZIN[26–29].

| Parameter | Base-case | Lower limit | Upper limit |
|---|---|---|---|
| Utility value PAV | 0.095 | -0.005 | 0.195 |
| Utility value not sitting and PAV free | 0.190 | 0.090 | 0.290 |
| Utility value sitting | 0.600 | 0.500 | 0.700 |
| Utility value walking | 0.850 | 0.750 | 0.950 |
| Monthly costs PAV | € 12,836 | € 10,269 | € 15,404 |
| Monthly costs not sitting and PAV free | € 12,836 | € 10,269 | € 15,404 |
| Monthly costs sitting | € 12,485 | € 9,988 | € 14,983 |
| Monthly costs walking | € 6,935 | € 5,548 | € 8,321 |
| One-time costs OA drug | € 2,195,905 | € 1,756,724 | € 2,635,086 |
| Discount rate costs | 0.040 | 0.000 | 0.080 |
| Discount rate outcomes | 0.015 | 0.000 | 0.030 |

*Table 6: Parameters tested in DSA.*

Additionally, a DSA is conducted to examine the uncertainty around the parameter distribution. The lower and upper limits of the parameters are obtained from Rstudio. In each transition, except for those following exponential distributions, the most extreme scenario is considered, using the lower limit of the shape/meanlog combined with the upper limit of the rate/sdlog parameter and vice versa. This approach aimed to capture the full range of variation between these two extremes. In Table 7 the lower and upper limits of the parameters are shown.

| Health state transition | Distribution | Base-case | Lower limit | Upper limit |
|---|---|---|---|---|
| **PAV - dead** | *Exponential* | | | |
| *intercept* | | -1.711591 | -2.217652 | -1.205531 |
| **sitting - dead (OA)** | *Gompertz* | | | |
| *shape* | | 0.05395975 | 0.04249996 | 0.06541955 |
| *rate* | | -5.240715 | -5.61661893 | -4.86481167 |
| **not sitting and PAV free - dead (BSC)** | *Log-normal* | | | |
| *meanlog* | | 0.2687879 | -0.2158845 | 0.7534602 |
| *sdlog* | | -0.2195602 | -0.7416484 | 0.302528 |
| **not sitting and PAV free - dead (OA)** | *Log-normal* | | | |
| *meanlog* | | 1.7455005 | 0.7349704 | 2.7560305 |
| *sdlog* | | 0.2861886 | -0.274327 | 0.8467041 |
| **not sitting and PAV free - PAV (BSC)** | *Exponential* | | | |
| *intercept* | | -1.998078 | -3.383982 | -0.6121747 |
| **not sitting and PAV free - PAV (OA)** | *Exponential* | | | |
| *intercept* | | -3.276512 | -4.408098 | -2.144927 |
| **not sitting and PAV free - sitting (OA)** | *Log-normal* | | | |
| *meanlog* | | 0.2211975 | 0.09381885 | 0.3485761 |
| *sdlog* | | -0.9406074 | -1.21221628 | -0.6689986 |
| **sitting - walking (OA)** | *Exponential* | | | |
| *intercept* | | -1.963025 | -3.348928 | -0.5771211 |

*Table 7: Lower and upper limits used for the DSA.*

### 3.4.2 Probabilistic sensitivity analysis

To assess the impact of parameter uncertainty, a PSA is conducted[50]. The PSA involves analyzing all uncertain parameters by defining appropriate probability distributions. While most parameter values are assumed to follow a normal distribution, exceptions are made for probability and utility values, cost inputs, and durations. For probability and utility values, which are constrained between 0 and 1, a beta distribution is deemed suitable. The beta distribution, characterized by parameters α and β, captures the number of events and non-events, respectively. When dealing with multinomial data, a Dirichlet distribution is preferred. Cost data tends to be skewed and constrained on the interval of 0 to infinity, so a gamma distribution is considered a better fit[50].

In addition to determining the appropriate distribution, it is necessary to justify the level of variability assigned to each parameter within the chosen distribution. The literature is a valuable source for obtaining the variance of each parameter, but in cases where data is unavailable, a standard deviation derived from a 20% variance assumption is used. Transition probabilities, on the other hand, utilize the Cholesky decomposition of variance. This is conducted for all transitions except the transition from the 'walking' to the 'dead' state. This exclusion is due to the fact that the data used for this analysis is sourced from national life tables[61], which eliminates the need for any extrapolation. Therefore this transition was not included as an uncertain parameter in the PSA.

Once the probability distributions and variances for each parameter are established, a random number is drawn from each distribution to calculate an ICER. This process is repeated 1000 times, generating multiple ICER values that are presented in a CE-plane. By repeating the ICER calculation for the indirect comparison between BSC and OA treatment and constructing the CE-plane in this manner 1000 times, a comprehensive understanding of the outcomes of the PSA is obtained. The number of iterations used in the PSA should be sufficient to achieve a stable and reliable result[51]. The PSA outcomes enable the estimation of the probability that each treatment option is cost-effective at different WTP threshold values. These probabilities are graphically represented in a CEAC and will be presented in the results section.

### 3.4.3 Scenario analysis/structural uncertainty

In order to provide an understanding of the potential effects of early treatment, a scenario analysis is incorporated based on the findings of the SPR1NT trial. The SPR1NT trial is a phase III, multicenter, single-arm study that aimed to assess the effectiveness and safety of OA in pre-symptomatic infants who were treated within six weeks of birth. All 14 infants from this trial that were in the published paper are included in the analysis. This scenario analysis aims to offer valuable insights into the (health and cost) benefits of early treatment with OA.

For the transition from 'not sitting and PAV free' state to 'sitting' and from 'sitting' to 'walking', published data from the SPR1NT trial is used. However, similar data sources from the base-case are employed for the remaining transitions. The reason behind this choice is that the extrapolations from pooled data from the SPR1NT trial and the NeuroNEXT trial showed shorter survival outcomes, which is contradictory since the SPR1NT trial demonstrates more effective results compared to the STR1VE trials (see Appendix 2 – extrapolations SPR1NT trial). This is due to the fact that the sample size is smaller compared to the base-case, hence more uncertainty. Therefore, to ensure more reliable and consistent results, the same sources that are used in the base-case are used for the other transitions, which had a larger sample size.

The same approach for the extrapolation of the health state transitions is employed as in the base-case to extrapolate from 'not sitting and PAV free' to 'sitting', and from 'sitting' to 'walking'. Visual inspection and AIC and BIC tests are utilized to determine the most suitable parametric distributions for these transitions. A Gompertz distribution is selected as the best fit for the transition from 'not sitting and

PAV free' to 'sitting', while a Weibull distribution is chosen for the transition from 'sitting' to 'walking' (Figure 3). The AIC and BIC test results are shown in Appendix 1 – AIC and BIC overview.

a) not sitting and PAV free → sitting (SPR1NT)

b) sitting → walking (SPR1NT)

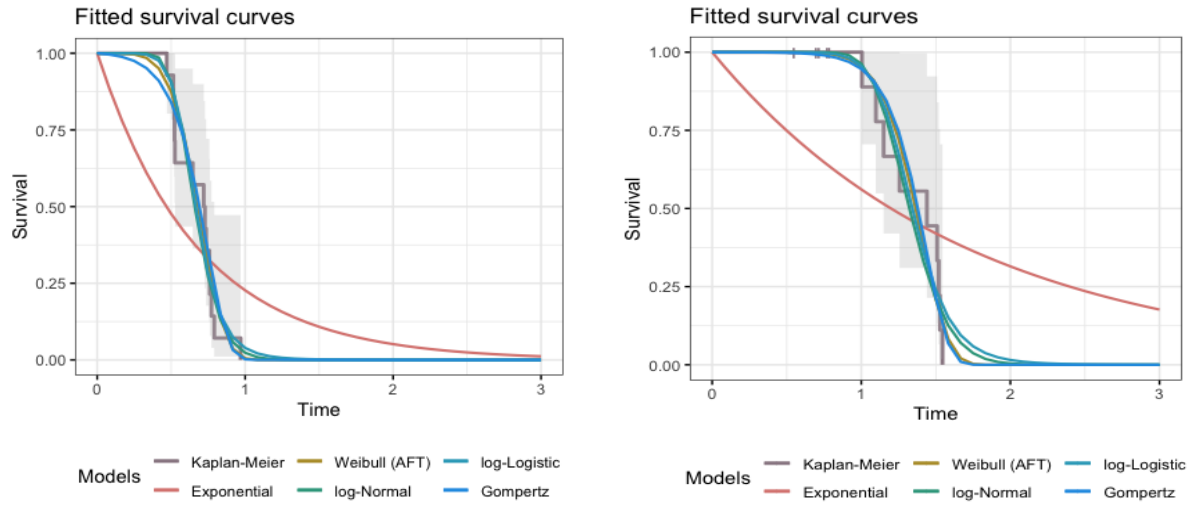



*Figure 3: Extrapolation of health state transitions based on the SPR1NT trial.*

# 4. Results

## 4.1 Outcomes base-case

### 4.1.1 Markov traces

Using the selected extrapolated parametric distributions presented in Table 2 and employing a cohort simulation with 1000 patients, it is possible to fill the Markov traces for each treatment group in the model. Figure 4 illustrates the Markov trace for the BSC arm, while Figure 5 shows the Markov trace for the OA treatment arm. Examination of the Markov traces reveals that patients receiving the OA treatment experience improvements in motor skills, including sitting and walking independently, which are not achievable with BSC alone. Additionally, the OA treatment arm demonstrates a higher age at the time of death. The traces showing the proportion of patients in the 'PAV' health state and those in the 'not sitting and PAV free' state appear to exhibit similar patterns in both figures. From these Markov traces, it can be concluded that the OA treatment shows improvements in disease prognosis, with motor skill achievement, and delayed age of death when compared to the standard treatment, BSC.

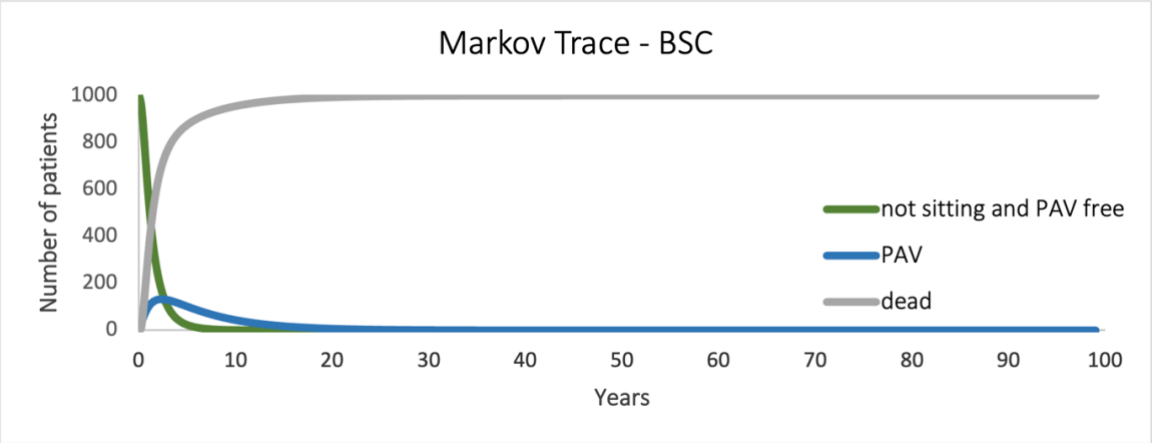



*Figure 4: Markov traces of the BSC arm.*

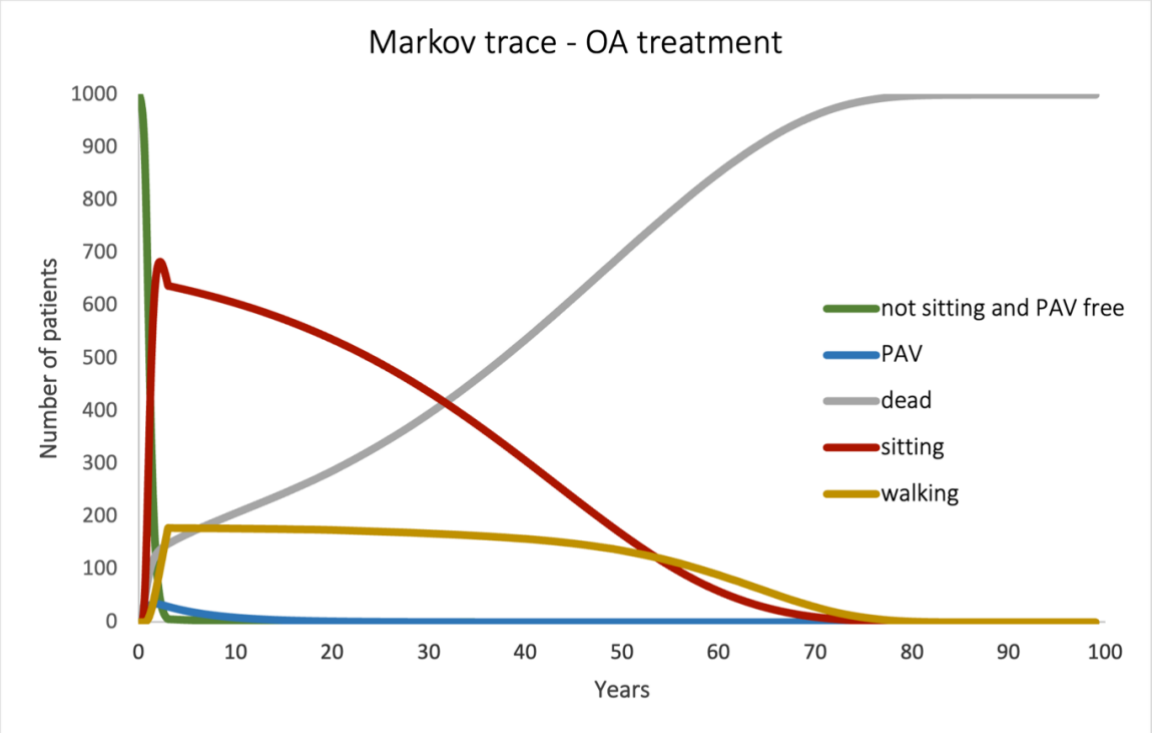



*Figure 5: Markov traces of the OA treatment arm.*

### 4.1.2 Incremental costs and effects

The results of the cost-effectiveness analysis are presented in Table 8. In the base-case, the total costs for the standard treatment, BSC, contain €350,878, while the costs for the alternative treatment, OA, are €4,386,381. This results in incremental costs of €4,035,503. The LY gained by the standard treatment is 2.46 years, whereas OA treatment provides a substantial increase of 25.05 LY, resulting in incremental LY of 22.58. Similarly, when considering the QALYs, BSC results in 0.37 QALYs, while OA shows a significant improvement with 16.03 QALYs. This leads to incremental QALYs of 15.66. The ICER is calculated as €257,717 per QALY gained.

| Outcomes base-case | |
|---|---|
| **Costs (€)** | |
| BSC | € 350,878 |
| Onasemnogene abeparvovec | € 4,386,381 |
| Incremental costs | € 4,035,503 |
| **Life years** | |
| BSC | 2.46 |
| Onasemnogene abeparvovec | 25.05 |
| Incremental life years | 22.58 |
| **QALYs** | |
| BSC | 0.37 |
| Onasemnogene abeparvovec | 16.03 |
| Incremental QALYs | 15.66 |
| **ICER (€/QALY)** | **€ 257,717** |

*Table 8: base-case outcomes from a societal perspective.*

## 4.2 Outcomes sensitivity analysis

### 4.2.1 Probabilistic sensitivity analysis

The outcomes of the PSA are shown in the CE-plane in Figure 6. All of the ICERs obtained from the analysis fall within the northwest quadrant, indicating that the OA treatment carries higher incremental costs and incremental QALYs compared to BSC. The probability of the OA treatment being considered cost-effective at a WTP threshold of €80,000 per QALY gained is zero, as none of the ICERs from the PSA fall below this threshold line.

Moreover, examining the CE-plane in Figure 6 reveals notable variation in the incremental QALYs. The incremental QALYs span over an interval of 11 to 23. The incremental costs exhibit significant variability, ranging between approximately 3 and 5 million euros.

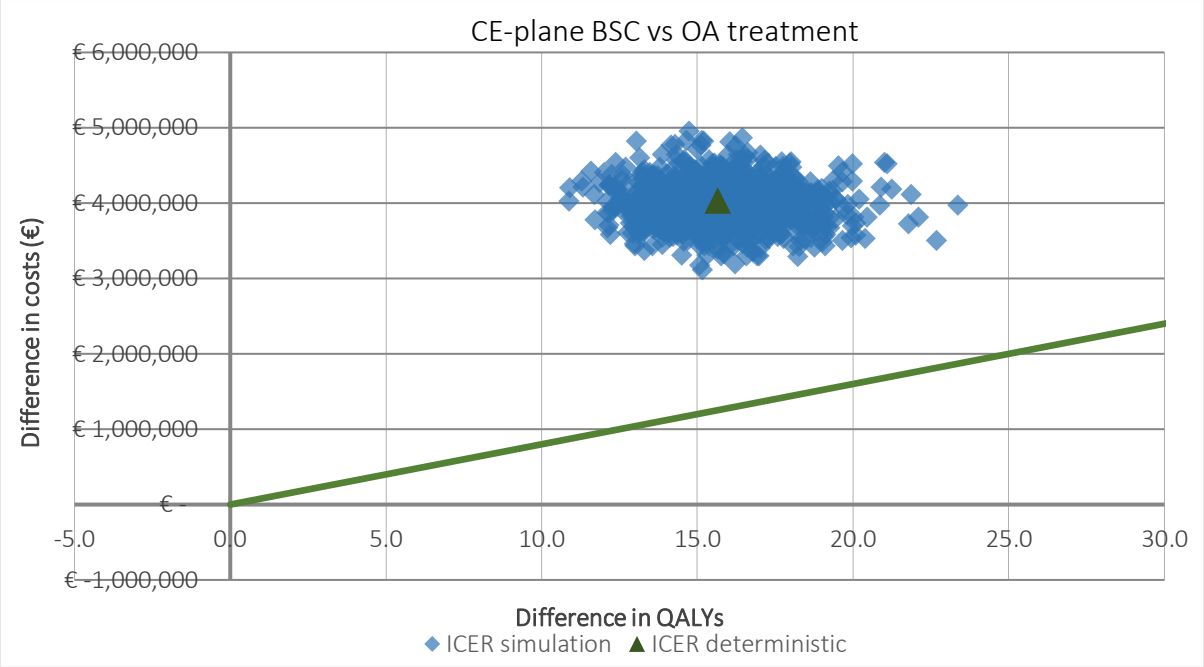



*Figure 6: Cost-effectiveness plane based on the PSA.*

In Figure 7, the CEAC is presented. The curve illustrates the relationship between the WTP threshold and the probability of the intervention being considered cost-effective. The point where the lines intersect, at a threshold value of €255,000, represents the critical threshold at which both treatment arms have an equal probability of being cost-effective.

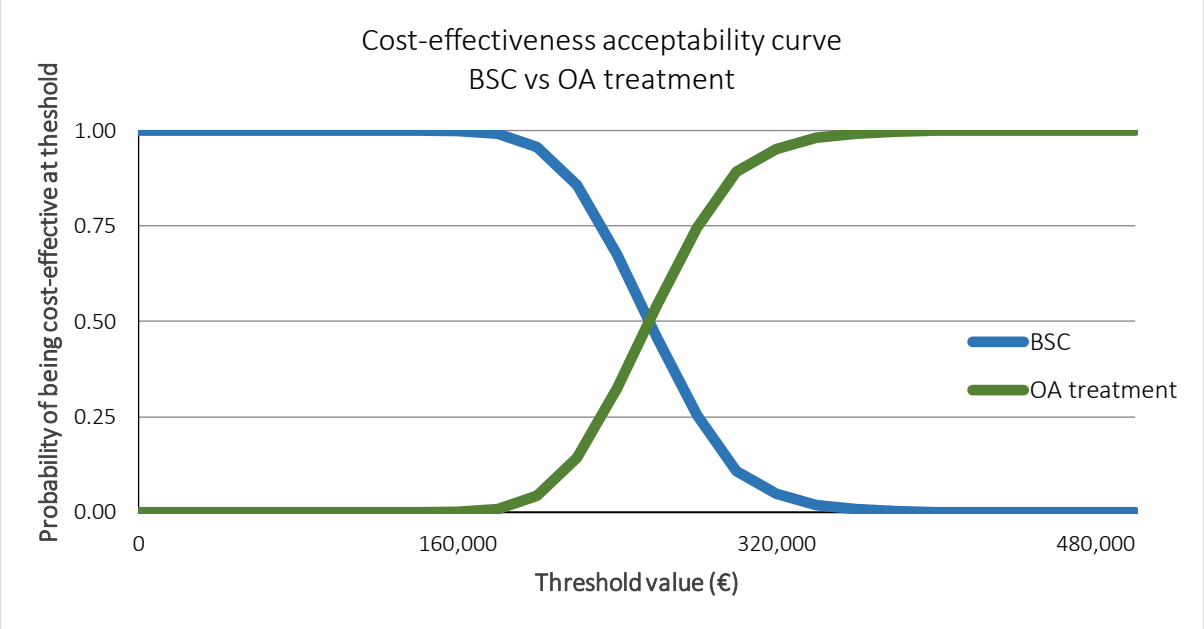



*Figure 7: cost-effectiveness acceptability curve.*

### 4.2.2 Deterministic sensitivity analysis

The tornado diagram in Figure 8 displays the outcomes of the DSA. Variations in discount rates strongly influence the ICER, with the discount rate applied to costs playing a particularly crucial role. The ICER is also sensitive to changes in the cost and utility values associated with sitting and the cost of the drug (OA). The ICER is quite sensitive to assumptions made in these input parameters. However, the ICER never falls below the threshold value of €80,000 as it varies between €180,000 and €400,000 per QALY

gained. The tornado diagram indicates that the ICER is moderately affected by alterations in the costs and utility values associated with the 'walking' health state. While these changes influence the ICER, their impact is relatively minor compared to the significant effect observed with the discount rates, utility, and cost values of 'sitting' and costs of the drug OA. Changes in the cost and utility values of the 'not sitting and PAV free' scenario and the 'PAV' health state have minimal influence on the ICER.

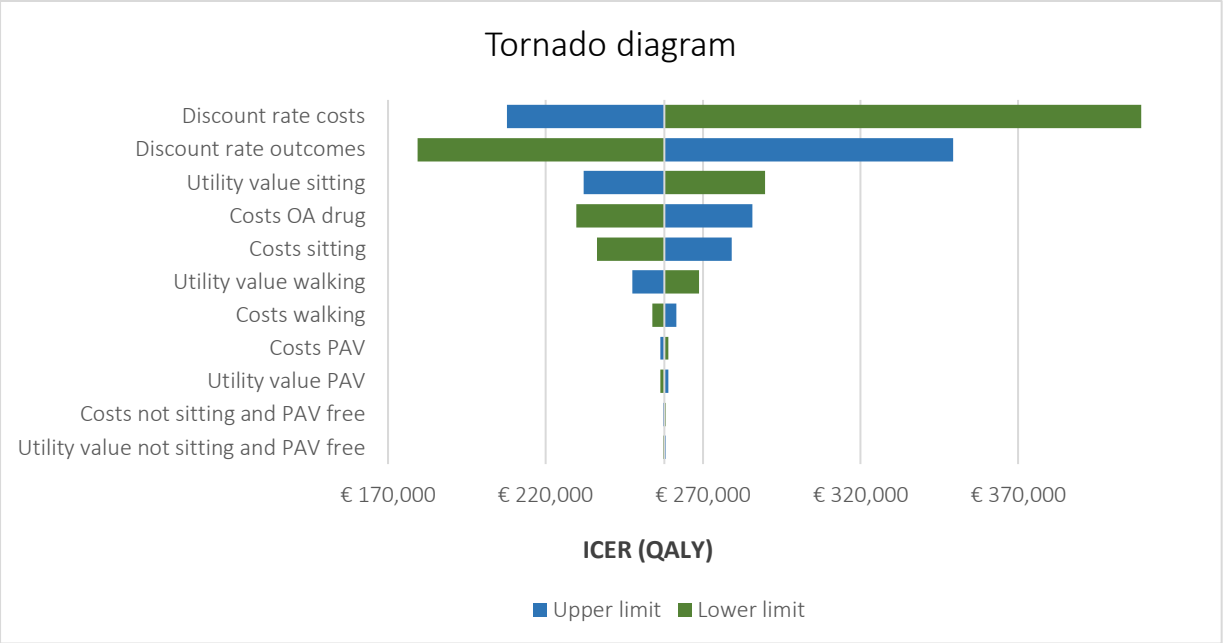



*Figure 8: Outcomes of the deterministic sensitivity analysis presented in a tornado diagram.*

Figure 9 presents a tornado diagram displaying the extreme values of the upper and lower limits of the parameters from the extrapolations used for the DSA. The diagram shows that the extrapolation of the transition from 'sitting' to 'walking' exhibits is highly sensitive to changes in the parameters. Additionally, moderate changes are observed in the transitions from the OA treatment arm. Overall, it is apparent that the extrapolations for the OA treatment arm alone are more susceptible to variations compared to the extrapolation for the BSC arm. However, less uncertainty is shown in the parameter variations compared to the discount rate changes.

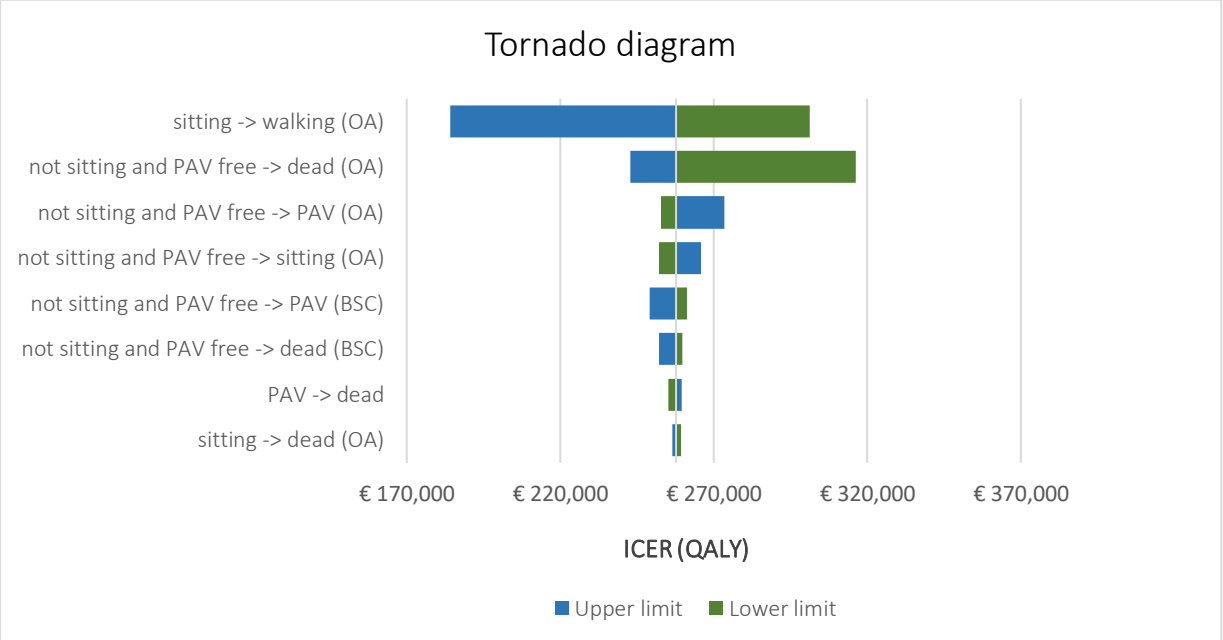



*Figure 9: Outcomes of the deterministic sensitivity analysis presented in a tornado diagram.*

### 4.2.3 Outcomes scenario analysis

Table 9 presents the scenario analysis results, which incorporated findings based on the SPR1NT trial to evaluate the effectiveness of pre-symptomatic treatment. A comparison with the base-case reveals significant differences: the incremental LYs and QALYs are higher in the scenario analysis, with values of 31.96 and 28.33, respectively, compared to 22.58 and 15.66 in the base-case. The incremental QALYs in the scenario analysis show an 81% increase compared to the base-case (LYs show a 41% increase). Also, the costs in the scenario analysis are slightly lower compared to the base-case. Additionally, the ICER in the scenario analysis is €127,107, representing a decrease of just over 50% compared to the base-case. Although the ICER from the scenario analysis still exceeds the threshold of €80,000, it is much closer to the threshold compared to the base-case.

| Outcomes scenario analysis | | |
|---|---|---|
| **Costs (€)** | **Base-case** | **SPR1NT** |
| BSC | € 350,878 | |
| Onasemnogene abeparvovec | € 4,386,381 | € 3,951,500 |
| Incremental costs | € 4,035,503 | € 3,600,622 |
| **Life years** | | |
| BSC | 2.46 | |
| Onasemnogene abeparvovec | 25.05 | 34.42 |
| Incremental life years | 22.58 | 31.96 |
| **QALYs** | | |
| BSC | 0.37 | |
| Onasemnogene abeparvovec | 16.03 | 28.70 |
| Incremental QALYs | 15.66 | 28.33 |
| **ICER (€/QALY)** | **€ 257,717** | **€ 127,107** |

*Table 9: Outcomes of the scenario analysis.*

# 5. Discussion

## 5.1 Discussion of the results

Interpreting the results of the cost-effectiveness analysis, the use of the drug OA compared to BSC shows promising outcomes with incremental QALYs of 15.66 and an ICER of €257,717. Through the Markov traces, it becomes evident that patients receiving the OA treatment experienced significant improvements in motor skills, such as sitting and walking independently, which were not achievable with BSC alone. Moreover, the OA treatment arm demonstrates a delayed age of death, indicating potential benefits in terms of longevity.

In terms of cost-effectiveness, the base-case scenario reveals higher costs associated with the OA treatment compared to BSC. However, the OA treatment also provides substantial increases in LY and QALYs, 22.58 and 15.66, respectively, indicating better health outcomes. The high costs of the OA treatment are influenced not only by the significant one-time cost of the treatment itself, which amounts approximately €2 million, but also by the fact that the total treatment costs of SMA increase as patients live longer. Patients receiving the OA treatment have a considerably longer life expectancy (25.05 LY) than those receiving the standard treatment, BSC (2.46 LY). This extended lifespan is associated with monthly costs incurred over a more extended period. In contrast to BSC, where monthly costs are incurred for a significantly shorter duration. The ICER was calculated to be €257,717 per QALY gained.

The PSA also confirmed that OA is more cost-effective than BSC, as all ICERs fall within the northwest quadrant of the CE-plane (Figure 6). This quadrant indicates higher incremental costs and QALYs for the OA treatment compared to BSC. None of the incremental ICERs from the PSA reached a threshold value below €80,000 per QALY gained, suggesting that the OA treatment is not considered cost-effective at this threshold. The DSA provides further insights into the robustness of the results. The analysis demonstrates that the ICER is highly sensitive to variations in discount rates, the drug's costs, and the cost and utility values associated with ‘sitting’.

Changes in the discount rates significantly affect the ICER. This can be attributed to the model's time horizon encompassing 99 years, making discount factors have a more pronounced effect on long-term models compared to shorter ones[48]. When the discount rate for costs is set to 0, there is a 59% increase in the ICER. This can be attributed to the prolonged lifespan resulting from the administration of OA to patients and the corresponding sustained high costs.
The uncertainty surrounding the utility and cost parameters related to the health state ‘sitting’ can be attributed to the fact that, after the short-term model (in the OA treatment arm) of 36 months, a substantial proportion of patients (slightly over 60%) remain in this health state, which significantly influences both LY and associated costs. As a result, any changes in the cost and utility parameter values associated with ‘sitting’ strongly impact the overall model. Over time, a proportion of these patients slowly transition to the states of ‘dead’ or ‘PAV’. The high uncertainty surrounding the costs of OA, known as one of the most expensive drugs in the world, can be attributed to the proportionally significant impact of a 20% change in costs. Given the substantial magnitude of the costs, it is logical that even a relatively ‘small change’ can have a considerable influence on the ICER. However, it should be noted that despite a price reduction of 20% resulting in an ICER of €229,668, the values are still unlikely to fall below the threshold value of €80,000.
On the other hand, changes in the cost and utility values of the ‘walking’ health state have a moderate effect on the ICER, and changes in the cost and utility values of the ‘not sitting and PAV free’ and the ‘PAV’ health state have minimal influence. This can be explained by a smaller proportion of individuals occupying the specific health state, leading to their reduced influence on the model's calculation of LY and costs. Nevertheless, these uncertainties suggest that accurate estimation of these parameters is crucial when evaluating the cost-effectiveness of the OA treatment.

The parameter variations of the extrapolations reveal significant differences between the transitions from 'sitting' to 'walking' and from 'not sitting and PAV free' to 'dead'. These transitions exhibit substantial changes, indicating that the uncertainty in extrapolations of the OA treatment arm outcomes is more significant compared to the BSC approach. Other OA treatment parameters also display some changes, although to a lesser extent. These findings suggest that, in general, the extrapolations of the OA treatment arm are associated with higher levels of uncertainty than those of the BSC approach. The small sample size and short follow-up time could be an explanation for these results

The scenario analysis, which takes into account the published findings of the SPR1NT trial, demonstrates promising outcomes. The analysis reveals that pre-symptomatic treated patients are likely to derive greater benefits from OA than symptomatic treated patients, as indicated by higher LY and QALYs and less costs than the base-case. Furthermore, this leads to a lower ICER compared to the base-case, indicating that pre-symptomatic treatment with OA is more cost-effective. However, it is important to note that the ICER of €127,107 still exceeds the WTP threshold of €80,000. While these results are positive for the treatment of pre-symptomatic patients, it is currently unknown to what extent OA provides benefits because there is no available comparative data for individuals with pre-symptomatic SMA who have not undergone OA treatment. Nevertheless, these findings provide evidence of the advantages of early treatment with OA.

## 5.2 Comparing results to previous studies

### 5.2.1 ZIN report OA (2021)

The results from this study are compared to the alternative base-case from the ZIN report published in 2021, as it used the same cost methodology as this analysis[28]. The incremental costs obtained are €4,035,503, comparable to those reported in the ZIN report, which amounted to €4,149,822[28].

Regarding the BSC arm, slightly higher BSC costs are observed (€350,878) compared to the ZIN report (€255,112)[28]. This discrepancy can be attributed to variations in the choice of survival distribution, cycle length (monthly versus 6-month cycles), and a minor attribution to inflation.
Examining the LY and QALYs for the BSC arm, the results show slightly higher LY (2.46) and QALYs (0.37) compared to the ZIN report (LY: 2.28, QALYs: 0.21)[28]. This can be explained by the same factors influencing the costs, such as the choice of survival distribution and cycle length. Since the same datasets are used for the BSC arm, these discrepancies can also be attributed to methodological variations.
More substantial differences are observed in comparing the results of LY and QALYs between the ZIN report for the OA arm. In this analysis, the OA arm showed a higher LY of 25.05 and incremental LY of 22.58, whereas the ZIN report reported values of 19.95 and 17.66, respectively. Similarly, higher QALYs of 16.03 and incremental QALYs of 15.66, whereas the ZIN report reported values of 12.00 and 11.79, respectively[28].
These findings are particularly promising considering that a different dataset is used, excluding the START trial and incorporating the STR1VE-EU trial. The STR1VE-EU trial demonstrated promising results and contributed to reducing uncertainty due to its larger sample size[18]. It is important to note that a relatively short follow-up time is used due to the 18-month follow-up period in the STR1VE trials. Nevertheless, the results demonstrate higher LY and QALYs, indicating the potential benefits of treatment with OA.

Comparing the ICERs of the analysis (€257,717 per QALY gained) and the ZIN report (€352,095), a significant reduction of almost 27% is observed. The lower ICER suggests a more favorable cost-effectiveness profile for treatment with OA. Despite the significant reduction, the calculated ICER of €257,717 remains considerably high and is above the WTP threshold of €80,000 used in the Netherlands.

It is important to acknowledge that variations in assumptions, data sources, or methodological approaches between these analyses may contribute to the observed differences in ICERs. Nonetheless, the notable reduction in the ICER indicates the potential cost-effectiveness of OA treatment compared to BSC and strengthens the case for its consideration in healthcare decision-making processes.

### 5.2.2 Other literature

The Dutch cost-effectiveness analysis from Broekhoff et al. (2021) presents challenges for direct comparison due to differences in model structure, and the exceptionally high utility values used (Table 3) further complicates the interpretation[21]. Additionally, the research included only the START trial with a sample size of 12 patients for the OA arm, leading to more uncertainty regarding the results. However, when considering a broader perspective, the overall findings support the notion that OA treatment is cost-effective compared to BSC, as indicated by an ICER of €138,875, which is still above the WTP threshold in the Netherlands[21].
In contrast, the Australian cost-effectiveness analysis from Wang et al. (2022) employed the same Markov model. But diverged in cost calculations and the use of conservative utility values (Table 3), making direct comparisons challenging[22]. The ICER of OA treatment in the Australian cost-effectiveness analysis is $1,808,471, which is considerably higher compared to the results obtained in this analysis. Nevertheless, the results from the Australian study support the idea that OA treatment leads to health benefits compared to BSC. Yet, it is unlikely to meet the commonly accepted cost-effectiveness thresholds in Australia[22]. Moreover, differences in clinical practice between Australia and the Netherlands might also explain differences in results.

In summary, while the analyses conducted in both the Dutch and Australian contexts suggest positive outcomes and health benefits associated with OA treatment compared to BSC, it is evident that the cost-effectiveness of OA may not align with the established WTP thresholds in these respective settings.

## 5.3 Strengths and limitations

### 5.3.1 Methodology

*Outcome uncertainty*

The use of outcomes from separate studies with variations in patient populations at baseline, differing prognoses, and age at treatment initiation introduce significant uncertainty in the economic model. Due to the limited number of patients in the clinical studies, conducting subgroup analyses is not possible. The uncertainty is exacerbated by the inclusion of different natural history studies with various methods used in the economic model.

It is important to consider that the natural historical controls, particularly in older natural history studies, may downplay the perceived treatment effect, especially when standards of care improve over time[68]. For instance, old natural history studies report a higher mortality rate of around 68% for patients with Type I SMA at two years of age. In contrast, recent estimates show improved survival rates of approximately 30% at that age, partly due to advancements in nutritional and respiratory support[27].

In the OA treatment arm, the short-term model (first three years) relies on a small number of patients from the STR1VE-US and EU trials. This limited sample size raises concerns about the generalizability of these findings to a broader population of SMA patients. Those ineligible or not selected for the trials might have been more severely ill, experienced different or additional comorbidities (e.g., scoliosis), or had a different genetic profile compared to the participants in the clinical trials. However, it is worth noting that the sample size in this study for the OA treatment arm is larger compared to previous cost-effectiveness studies, providing more robust results.

While a short-term model of 36 months is used, it is essential to acknowledge that the STR1VE-US/EU trials, from which the data is derived for the OA treatment arm, have an 18-month follow-up. This short follow-up time introduces additional uncertainty to our findings.

Moreover, there is a lack of long-term data on the safety and efficacy of OA treatment. Although the currently-available data do not indicate a diminishing benefit, it is crucial to recognize that understanding the long-term effects of OA treatment will require more time due to the rarity of SMA and the short follow-up periods in the trials. Uncertainty exists regarding the duration of expression of the novel gene therapy and its potential to offer lifelong benefits to patients.

Overall, these limitations underline the challenges associated with incorporating outcomes from different studies, considering (old) natural history controls, the impact of sample size and eligibility criteria, the need for long-term data, and the uncertainties surrounding the duration of therapeutic effects.

### 5.3.2 Parameter assumptions

*Assumption costs*

As mentioned in section 3.3.5 there is a lot of uncertainty about the cost of SMA. The costs used in the analysis are similar to those employed in the ZIN report of nusinersen and the alternative base-case in the ZIN report of OA[28,39]. These costs were derived from a study by Klug et al. (2016) [66]. In this study, SMA type II and SMA type III serve as proxies for treated SMA type I patients. Comments of the Review Group, which provided feedback on the ZIN report of OA, identified this approach as problematic, as it may lead to an underestimation of the costs involved. However, the Review Group acknowledged that the costs from the Klug et al. (2016) study serve as a more appropriate and reliable data source than those used in the base-case analysis[28].

*Assumption utility values*

The method section 3.3.4 mentions the significant uncertainty associated with the utilities selected for the health states. This uncertainty arises due to two main reasons. Firstly, available data are scarce specifically for a rare disease population. Secondly, the methodological challenges in assigning utility values to young children further contribute to this uncertainty. However, based on feedback from previous reports, the selected utility values were determined to be the most appropriate for the respective health states. These values represent an improvement towards approximating the true value.

*Assumption SE*

An estimated standard error of 20% variance was utilized, when de standard error of the parameter was unknown. However, this estimation may not accurately reflect the actual variability of parameters and could have led to PSA results that might be unreliable.

## 5.4 Societal and scientific relevance of this research

No previous study has conducted a cost-effectiveness analysis based on the recently published STR1VE-EU trial, including a larger sample size. Consequently, the findings of this economic evaluation hold scientific significance. However, it is essential to note that this study did not incorporate the STRAT trial due to the unavailability of relevant data. Nonetheless, the results of this research demonstrate promising outcomes in terms of increased LY and a reduced ICER when compared to the alternative base-case analysis presented in the ZIN report.

Furthermore, this study stands out by not only incorporating the STR1VE-EU trial but also including the newly published outcomes from the SPR1NT trial, which no previous research has accomplished. This aspect provides a promising outlook on the benefits of early treatment and the (potential) value of implementing SMA in NBS programs.

Moreover, this research provides a comprehensive overview of the outcomes associated with OA treatment in SMA type I patients, incorporating newly available data and presenting promising results.

## 5.5 Suggestions for further research

There is significant uncertainty around the outcomes of this study, despite the inclusion of an additional trial in the base-case analysis. To reduce this uncertainty, future cost-effectiveness analyses should incorporate additional follow-up data to gain better insights into the long-term effects of OA treatment and potential adverse events. Additionally, including new clinical trials, thereby expanding the sample size, can also effectively decrease the level of uncertainty.

Furthermore, it would be valuable to conduct further research exploring the use of different natural history studies as comparators. The currently available natural history studies are outdated, and considering the improved prospects of standard care (BSC), utilizing more recent data would enhance the accuracy and relevance of cost-effectiveness evaluations.

# 6. Conclusion

Overall, the results of the cost-effectiveness analysis support the notion that the OA treatment offers significant improvements in disease progression, motor skills, and quality of life compared to BSC. Despite the higher costs associated with the OA treatment, the substantial gains in LY and QALYs demonstrate their potential value. Nevertheless, with an ICER of €257,717 at a threshold of €80,000 per QALY, the cost-effectiveness analysis indicates that OA is not a cost-effective option compared to BSC. The primary factors influencing the ICERs are the expenses associated with OA and the costs and utility values assigned to sitting. Lowering the costs or enhancing the utility values could significantly improve the cost-effectiveness of OA in comparison to BSC.
Furthermore, the scenario analysis presented promising outcomes regarding the benefits of pre-symptomatic treatment with OA. It supported the recommendation of the Dutch Health Council for incorporating SMA in the NBS program in the Netherlands.
The scarcity of evidence from clinical trials, with small sample sizes and short follow-up time, poses a significant challenge in developing economic models regarding SMA treatment. Additionally, exploring more suitable WTP thresholds in the context of rare diseases is crucial to inform reimbursement decisions within a predominantly publicly funded healthcare system.

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# 8. Appendices

## Appendix 1 – AIC and BIC overview

| | Treatment with OA | | | | |
|---|---|---|---|---|---|
| Statistical test | 'not sitting and PAV free' → 'sitting' | | | | STR1VE-trial |
| | Exponential | Weibull | **Log-normal** | Log-logistic | Gompertz |
| AIC | 91.662 | 57.260 | 55.207 | 56.908 | 60.984 |
| BIC | 93.399 | 60.735 | 58.683 | 60.383 | 64.460 |
| | 'sitting' → 'walking' | | | | STR1VE-trial |
| | **Exponential** | Weibull | Log-normal | Log-logistic | Gompertz |
| AIC | 13.852 | 14.191 | 13.696 | 14.095 | 14.940 |
| BIC | 15.148 | 16.782 | 16.287 | 16.686 | 17.532 |
| | 'not sitting and PAV free' → 'PAV' | | | | OA |
| | **Exponential** | Weibull | Log-normal | Log-logistic | Gompertz |
| AIC | 27.659 | 28.669 | 28.555 | 28.664 | 28.935 |
| BIC | 29.720 | 32.790 | 32.676 | 32.785 | 33.056 |
| | 'not sitting and PAV free' → 'dead' | | | | OA |
| | Exponential | Weibull | **Log-normal** | Log-logistic | Gompertz |
| AIC | 59.635 | 60.871 | 59.440 | 60.575 | 61.629 |
| BIC | 61.696 | 64.992 | 63.561 | 64.696 | 65.750 |
| | 'sitting' → 'dead' | | | | OA |
| | Exponential | Weibull | Log-normal | Log-logistic | **Gompertz** |
| AIC | 1726.192 | 1639.055 | 1662.759 | 1655.934 | 1636.828 |
| BIC | 1729.673 | 1646.017 | 1669.720 | 1662.895 | 1643.789 |

Table 1

| | Treatment with BSC | | | | |
|---|---|---|---|---|---|
| Statistical test | 'not sitting' → 'PAV' | | | | OA |
| | **Exponential** | Weibull | Log-normal | Log-logistic | Gompertz |
| AIC | 13.992 | 14.827 | 14.770 | 14.840 | 15.040 |
| BIC | 14.765 | 16.373 | 16.315 | 16.385 | 16.585 |
| | 'not sitting' → 'dead' | | | | OA |
| | Exponential | Weibull | **Log-normal** | Log-logistic | Gompertz |
| AIC | 29.760 | 30.086 | 27.755 | 28.512 | 31.538 |
| BIC | 30.533 | 31.631 | 29.300 | 30.057 | 33.083 |

Table 2

| | Treatment with OA & BSC | | | | |
|---|---|---|---|---|---|
| Statistical test | 'PAV' → 'dead' | | | | |
| | **Exponential** | Weibull | Log-normal | Log-logistic | Gompertz |
| AIC | 83.348 | 84.446 | 85.512 | 85.152 | 85.144 |
| BIC | 84.526 | 86.802 | 87.868 | 87.508 | 87.500 |

Table 3

## Appendix 2 – extrapolations SPR1NT trial

| | Treatment with OA – SPR1NT | | | | |
|---|---|---|---|---|---|
| Statistical test | 'not sitting and PAV free' → 'sitting' | | | | |
| | Exponential | Weibull | Log-normal | Log-logistic | **Gompertz** |
| AIC | 18.957 | -11.119 | -11.718 | -10.487 | -9.223 |
| BIC | 19.596 | -9.840 | -10.440 | -9.208 | -7.945 |
| | 'sitting' → 'walking' | | | | |
| | Exponential | **Weibull** | Log-normal | Log-logistic | Gompertz |
| AIC | 29.866 | -0.296 | 1.218 | 2.142 | -0.587 |
| BIC | 30.505 | 0.982 | 2.496 | 3.420 | 0.691 |
| | 'not sitting and PAV free' → 'PAV' | | | | OA |
| | Exponential | Weibull | Log-normal | Log-logistic | Gompertz |
| AIC | 17.556 | 18.841 | 18.851 | 18.860 | 18.835 |
| BIC | 18.957 | 21.644 | 21.653 | 21.662 | 21.638 |
| | 'not sitting and PAV free' → 'dead' | | | | OA |
| | Exponential | Weibull | Log-normal | Log-logistic | Gompertz |
| AIC | 42.881 | 43.767 | 42.305 | 43.282 | 44.753 |
| BIC | 44.282 | 46.570 | 45.108 | 46.084 | 47.556 |

Table 4

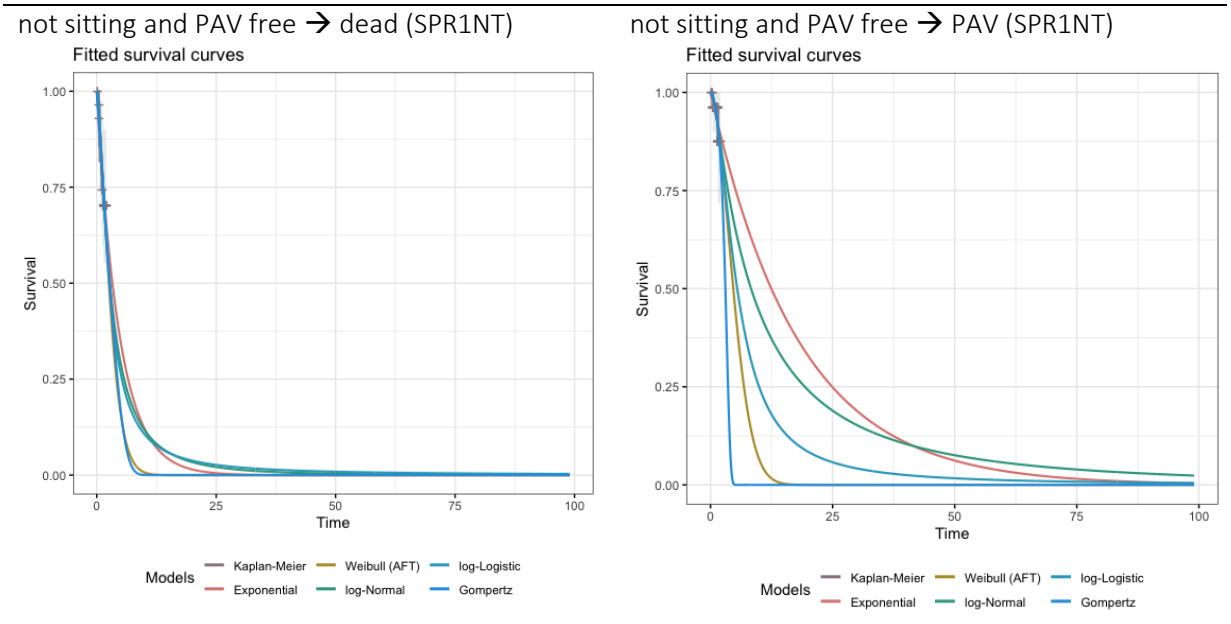


Figure 1