NEW ENGLAND CEPAC
AN ICER PROGRAM
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL

Nusinersen and AVXS-101 for Treatment of spinal muscular atrophy
Modeling Analysis Plan

November 5th, 2018

Institute for Clinical and Economic Review

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

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1. Approach

The aim of this economic evaluation is to estimate the cost-effectiveness of Nusinersen (Spinraza®, Biogen) and AVXS-101 (Investigational, AveXis), each compared to best supportive care (BSC) for patients with SMA from U.S. health sector and societal perspectives. We believe societal costs associated with SMA are substantial and large relative to the condition's health care costs, and will hence present base case results from both above mentioned perspectives, aligning with ICER's Value Assessment Framework for Ultra Rare Diseases. We will estimate the lifetime costs, life years gained and quality adjusted life years (QALYs) gained, discounted at 3% per annum, for each of the three treatment options and explore the cost-effectiveness of the nusinersen and AVXS-101 relative to BSC. Two *de novo* models will be developed: a model for symptomatic patients with SMA type 1 and a model for symptomatic patients with SMA type 2/3. These models will also be adapted to presymptomatic SMA Type 1 and presymptomatic SMA Type 2/3 patients; and will then be combined to estimate the cost effectiveness of presymptomatic SMA patients. The analytic framework for the models are depicted in Figures 1 and 2. The model will be developed in Microsoft Office Excel 2016 (Redmond, WA).

2. Methods

2.1 Overview and Model Structure

We will develop *de novo* decision analytic models for this evaluation, informed by key clinical trials[1-5] and prior relevant economic models.[6-10] The base case analysis will take a health care sector as well as a societal perspective aligning with ICER's Value Assessment Framework for Ultra Rare Diseases, as mentioned previously. Costs and health outcomes will be discounted at 3% per year.

The models will be dependent on three constructs: the motor function milestones gained; need for permanent ventilation; and the time to death. The motor function milestones used in the model(s) are sitting, walking and normal function. Other motor function milestones such as head control, rolling, crawling, and standing are not modelled as explicit health states in the model.

The models will contain two parts: (1) a short-term model concordant with clinical study data and (2) a long-term extrapolation model. A brief description of each is provided here with a detailed explanation of the data used is presented in subsequent sub-sections.

Short-term model

Data on motor function milestones, permanent ventilation, and mortality over different time points will be extracted from the relevant trials/studies (plus additional follow-up data from sources such

as open label extension studies and the follow up from trials). We do not expect to have adequate data to estimate transition probabilities. As such, the data for the different interventions during the study period will be used directly in the model to capture the proportion of the patients in the different health states at different points of time. These data will allow an estimate of the discounted costs and discounted QALYs for each of the three interventions (nusinersen, AVXS-101 and BSC) within the study periods.

Long-term model

The long-term model involves the extrapolation of motor function milestones, the need for permanent ventilation, and mortality which is assumed conditional on health states. The long-term model will use time cycles of 30.44 days (i.e. 365.25 days in year/12 months) to estimate the life time costs and QALYs.

The extrapolation of motor function milestones over a lifetime will be modelled using different scenarios. The base case scenario will assume that the motor function milestones achieved at the end of follow up in the clinical trials are sustained until death (i.e., patients stay in the same motor function milestone-based health state until death). In addition, an optimistic scenario for interventions where a proportion of patients will achieve additional motor function milestones and a pessimistic scenario (only for type 1 SMA patients) for the interventions where a proportion of patients will lose their milestones will also be modelled.

Transition to permanent ventilation state in the model is only possible for patients who do not have any motor function milestones i.e., the patients in the 'not sitting' health state. For these patients, both overall survival (OS) and ventilation-free survival (VFS) are modelled. All the other patients who have motor function milestones will not be considered at risk of transitioning to permanent ventilation.

The model will use state-specific mortality risks (i.e., a lower mortality risk for patients achieving motor function milestones). For the proportion of patients alive at the end of the short-term model, the long-term risk of mortality associated with each of the health states will be modelled by fitting survival curves to the digitized published Kaplan-Meier (KM) data most relevant to each health state. The KM data will be digitized, and the individual data will be reconstructed using the methods described in Guyot et al.[11] Different parametric distributions will be fitted to this survival data with the best fitting curves identified based on a combination of: visual inspection; fit statistics such as Akaike information criteria (AIC)/Bayesian information criteria (BIC); and clinical plausibility. For each health state, a single parametric distribution will be selected to calculate the estimated probability of death in each time period (e.g., a given month). The data on mortality risk associated with each health state are described in detail in section 2.5.

Figure 1. Model schematic for patients with SMA Type 1

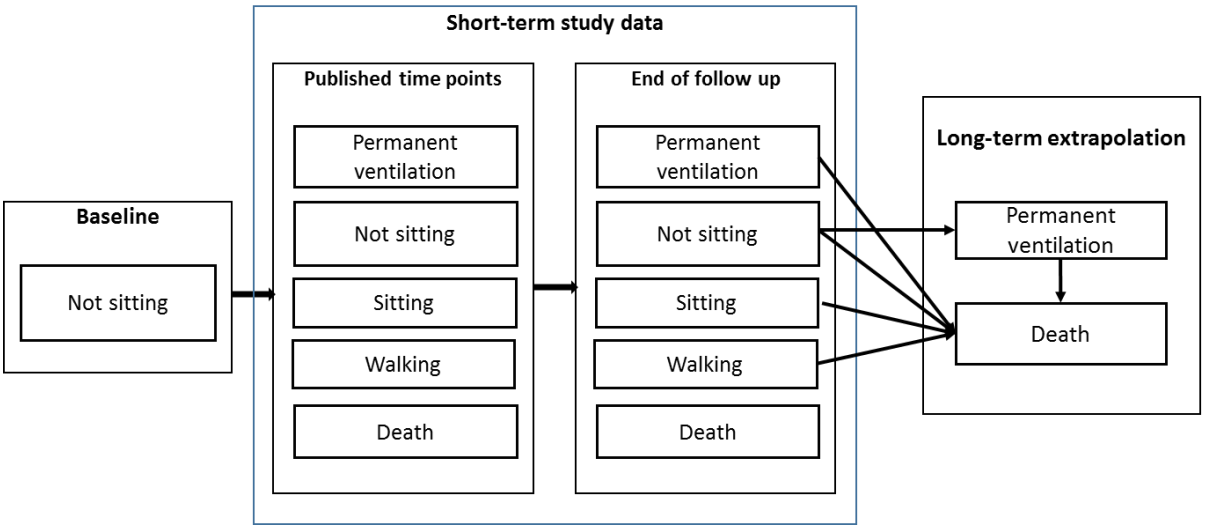
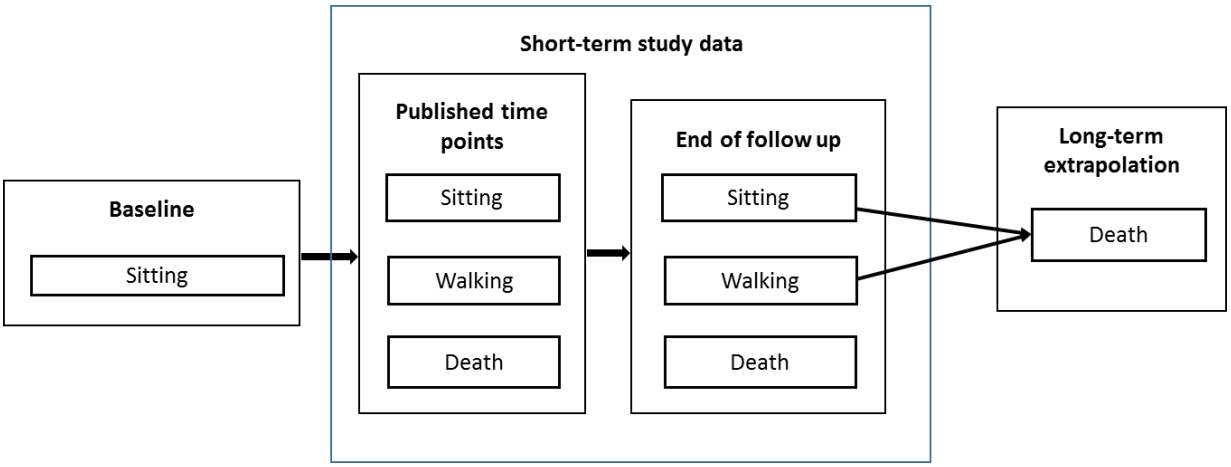


Figure 2. Model schematic for patients with SMA Type 2/3



2.2 Target Populations

The average age at treatment, gender distribution and mean weight of the SMA populations considered for the model are presented in Table 1, which are based on average values reported in the key clinical trials[1-3,5].

Table 1. Base-Case Model Cohort Characteristics

	SMA Type 1	Later Onset (SMA Type 2/3)	Pre-symptomatic SMA
Mean age	4.4 months	2 years	21 days
Female	55%	50%	52%
Mean weight	5.7 kg	-	-

2.3 Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The full list of interventions is as follows:

- Nusinersen, an FDA-approved (2016) treatment for SMA that is administered using intrathecal injection.
- AVXS-101, an investigational gene therapy currently under FDA review for approval, is potentially a one-time therapy administered using single intravenous infusion.

Comparators

The interventions will be compared to BSC, which involves standard respiratory, gastrointestinal, and nutritional care for SMA patients.

2.4 Key Model Choices and Assumptions

There are several assumptions for the base case model which are described below

Table 2. Key Model Assumptions

Assumption	Rationale
The analyses will use a naïve comparison between AVXS-101 and BSC, and nusinersen.	There are no head-to-head trials comparing AVXS-101 to the other interventions, and individual patient data (IPD) is needed to perform matched adjusted indirect comparisons or simulated treatment comparisons. As IPD was not provided, only a naïve comparison is possible i.e., the model compares the results of AVXS-101 to BSC and nusinersen without any adjustment using the nusinersen versus BSC trial.

Assumption	Rationale
Data from the trials/studies on motor function milestones, permanent ventilation and mortality is used directly in the short-term model.	Robust estimation of disease progression parameters (e.g. transition probabilities) is not possible without the access to IPD from the trials/studies. As such, the data for the different interventions during the study period will be used directly in the model to estimate short-term costs/QALYs.
Motor function milestones achieved at the end of the follow up are sustained until death.	There are no long-term data on the extrapolation of motor function milestones, and hence the base case analyses assume that these are sustained until death. However, alternative scenario analyses will also be considered.
Other motor function milestones such as head control, rolling, crawling, and standing are not modelled as explicit health states in the model.	The motor function milestones used in the model(s) are sitting, walking and normal function. However, scenario analyses will be undertaken to explore the potential impact of making allowances for different utilities within these broad health states.
Only patients in the 'not sitting' health state can move to permanent ventilation state.	Clinical experts opined that this is a reasonable assumption to make: that patients achieving motor function milestones are not at risk of permanent ventilation.
Patients with SMA type 1 who are in 'sitting' health state are assumed to have mortality similar to that of SMA type 2 patients.	Clinical experts opined that this is a reasonable assumption to make: that SMA type 1 Patients who can sit are assumed to have similar prognosis as SMA type 2 patients, who are able to sit but not walk.
Patients with SMA type 1 who are in 'walking' health state are assumed to have mortality similar to that of SMA type 3 patients.	Clinical experts opined that this is a reasonable assumption to make: SMA type I Patients who can walk are assumed to have similar prognosis as SMA type 3 patients, who are able to walk.
Patients on nusinersen who did not achieve motor function milestones at 12 months discontinue the treatment.	This is similar to the assumption used in the nusinersen model submitted to National Institute for Health and Care Excellence (NICE).

Assumption	Rationale
Utility data used in the base case analysis is derived from several sources.	There is no single source of utility data that is based on robust methodology and has face validity. Scenario analyses will be performed using other sources of utility data.
Adverse event costs and disutilities are not included in the model.	Given the nature of SMA, it is difficult to disentangle the adverse events due to treatment from the complications associated with SMA, which are already accounted for in the health state costs and disutilities. As such, the costs and disutilities of adverse events are not included in the model.
The costs of BSC are not included in the model.	Given the health state costs are already included in the model, and as the interventions are assumed to be on top of BSC, the costs of BSC are not included in the model.

2.5 Input Parameters

Clinical Inputs

The inputs for each of the short-term models (i.e., SMA type 1, SMA type 2/3, and presymptomatic) are presented first. The inputs for long term extrapolation are common across these models, and as such are presented together.

SMA Type 1 short-term model

Motor function milestones

The data on proportions of patients achieving motor function milestones at different time points for the different interventions are briefly presented below in Table 3, based on the ENDEAR trial[1] and SHINE study[2].

Table 3. Motor function milestones achieved on nusinersen

	Baseline n= 81	Day 64 n= 70	Day 183 n= 65	Day 302 n= 51	Day 394 n= 48	Day 578 n= 31	Day 698 n= 17
% achieving independent sitting (but not walking)	0	1	5	10	15	29	24
% achieving walking	0	0	0	0	0	0	0

None of the patients in the BSC arm are assumed to achieve any motor function milestones at any time points since the trial reported 0% of the patients in the sham control group achieved the ability to sit independently during assessment at Days 183, 302, or 394. We could not include longer-term data on this estimate in the BSC arm as all sham control patients in ENDEAR[1] switched to nusinersen treatment in SHINE, an open-label extension trial[2]. Doing so would attribute treatment benefit to BSC not associated with it.

For AVXS-101, we plan to use the data submitted to us by the manufacturer, but do not present it here due to it being academic-in-confidence.

Mortality

The proportions of patients who are alive at different time points are estimated from the OS data presented for each intervention.

The OS data for nusinersen are those of patients who received nusinersen in both ENDEAR[1] and SHINE[2]. The OS data for BSC are those from patients who received sham control in ENDEAR but only the data until the end of ENDEAR trial period is used in the model. This is because all sham control patients switched to nusinersen in SHINE[2] and including this would attribute survival benefit to BSC that isn't attributed to BSC.

None of the 12 patients receiving AVXS-101 in the single arm study[5] died at the last follow up of 24 months and as such this is reflected in the model. Given the small sample size, it may be mis-representative of real-world scenarios to assume that no patients on AVXS-101 will ever die in the short-term model. As such, scenario analyses will be performed using a continuity correction factor.

Permanent ventilation

The VFS rates at different time points are estimated from the combined VFS data in ENDEAR[1] and SHINE[2] and subtracted from the OS data to estimate the proportion of patients under permanent ventilation for the nusinersen arm.

The VFS data for BSC is from patients who received sham control in ENDEAR[1] alone. We do not use data from SHINE[2] since these sham control patients in ENDEAR[1] were switched to nusinersen in SHINE.

None of the 12 patients receiving AVXS-101 in the single arm study[5] received permanent ventilation at the last follow up and this is reflected in the model.

SMA Type 2/3 short-term model

Motor function milestones

The later onset SMA short term model will assume that the nusinersen patients remain in the 'sitting' health state until the end of the short-term model, based on trial data[4] where none of the patients achieved the ability to walk independently and only a fraction of patients who could sit were able to walk with assistance.

Trial results showed that none of the patients in the sham control arm achieved the ability to walk independently or walk with assistance[4]. As such, the model will assume that the BSC patients remain in the 'sitting' health state until the end of the short-term model.

Presymptomatic SMA short-term model

Effectiveness of nusinersen in achieving motor function milestones in pre-symptomatic patients will be captured from NURTURE study[3]. The models for symptomatic SMA Type 1 patients and symptomatic Type 2/3 patients will be adapted to estimate the costs and QALYs for Type 1 and Type 2/3 presymptomatic patients, respectively. The costs and QALYs for presymptomatic patients will be estimated as weighted average of costs/QALYs from the SMA Type 1 model and the later onset SMA model, using the proportions of patients with SMA Type 1 and SMA Type 2/3.

Hypothetical exploratory analyses will also be performed using assumptions around the efficacy of AVXS-101, in presymptomatic SMA patients.

Inputs for the long-term model

Extrapolation of motor function milestones

Motor function milestones in the long-term model will be extrapolated based on milestone status at the end of the short-term model with a base-case assumption that milestone status remains the same until death.

As mentioned earlier we will model two additional scenarios, an optimistic and a pessimistic where motor function milestones improve or deteriorate over time, respectively. The optimistic scenario will assume that a proportion of patients in the 'sitting' health state will achieve 'walking', and that a proportion of patients in the 'walking' health state achieves 'normal functioning'. The pessimistic scenario (for SMA type 1 patients only) will assume that a proportion of patients lose their motor function milestones. These assumptions i.e., the proportions of patients and the timing of these transitions will be validated with clinical experts for face validity.

Extrapolation of mortality

Mortality in the 'permanent ventilation' state

We use retrospective data[12] of SMA 1 patients from four Italian centers from October 1992, to December 31, 2010 to model mortality in the "permanent ventilation' health state. We will use data from two patient cohorts reported in this retrospective study: a) patients with continuous non-invasive respiratory muscle aid, including non-invasive ventilation; and mechanically assisted cough (n = 31) and, b) patients with tracheostomy and invasive mechanical ventilation (n=42). The proportions of SMA patients receiving these two types of interventions in the US will be used to estimate the weighted survival for patients in the 'permanent ventilation' state.

Mortality from 'sitting' state

Treated SMA type 1 patients who can sit are assumed to have similar prognosis as SMA type 2 patients, who are able to sit but not walk. Pooled data from German and Polish studies on SMA type 2 patients (n=240) presented in Zerres and Schöneborn et al[13] are used to model the mortality from the 'sitting' state.

Mortality from 'walking' state

Treated SMA type 1 patients who can walk are assumed to have similar prognosis as SMA type 3 patients, who are able to walk. A previously conducted study[13] reported no significant reduction in lifespan among SMA type 3 patients. As such, we will use the general population mortality for SMA type 1 patients who can walk.

Mortality from 'normal functioning' state

Patients achieving the 'normal functioning' milestone are assumed to have the general population mortality. It should be noted that there is no difference in mortality rates between patients who can walk and those with normal functional status.

Permanent ventilation and death from 'not sitting' state

As described earlier, patients from the 'not sitting' state can transition to either the 'permanent ventilation' health state or to death. We will use estimates from a longitudinal, multicenter, prospective natural history study NeuroNEXT[14] of SMA 1 patients to model these transitions in the long-term model. Data on time to death or intubation for patients with SMN2 copies of two or unknown will be used. The proportions of patients dying from this health state are estimated from the OS curve of NeuroNEXT study[14]. At each monthly cycle, the VFS curve is subtracted from the OS curve to estimate the proportion of patients in 'permanent ventilation' state.

Health State Utilities

Patient utilities

The utilities used in the base case analyses are derived from different sources, as presented in Table 4. The utilities from Batisda et al[15] are used for the 'permanent ventilation' and 'not sitting' health states, which were assumed to have same utility values (Note that we are intending to account for disutility of permanent ventilation, and are reviewing the literature for relevant data on this estimate). The utility for 'sitting' health state is captured from Tappenden et al[16]. The utilities for 'walking' and 'normal function' health states are captured from Thomson et al[17] which report the mapped values to PedSQL data from CHERISH [4], as the patients in the mapping study were all healthy patients.[18]

Table 4. Patient Utility Values for Health States

	Utility Value	Source
Permanent ventilation	0.19	Bastida et al., 2017[15]
Not sitting	0.19	
Sitting	0.60	Tappenden et al., 2018[16]
Walking	0.878	Thomson et al., 2017[17]/CHERISH[4]
Normal function	0.878	

Scenario analyses are also performed using utility data from each of the sources separately, the utilities data extracted from these studies are summarized in Table 5.

Table 5. Patient Utility Values for Scenario Analyses

	CHERISH [4]/ Thomson et al., 2017 [17]	Lloyd et al., 2017 [19]	Batisda et al., 2017 [15]	Tappenden et al., 2018 [16]
Permanent ventilation	0.730	-0.33	0.19	0.19
Not sitting	0.756	-0.12	0.19	0.20
Sitting	0.764	-0.04	0.1	0.60
Walking	0.878	0.71	0.54	0.85
Normal function	0.878	0.72	0.54	0.85

Caregiver utilities

The caregiver utilities are sourced from Bastida et al 2017[15], who surveyed 81 caregivers of patients with different subtypes of SMA in Spain. Out of 81 patients, eight had SMA type 1, 60 had SMA type 2 and 13 had SMA type 3. Bastida et al[15] report that the mean utility of all caregivers, estimated using EuroQol five dimensions (EQ5D) questionnaire with time trade off method, as 0.484. They also reported the mean utility value for Type 2 patients as 0.472, as presented in Table 6. Given the very low utility values reported, there are concerns with the face validity of this data. We plan to use a baseline utility for caregivers of patients in the 'not sitting' state and assume a slope of increasing utility for caregivers of patients achieving further milestones.

Table 6. Caregiver Utility Values

Health State	Utility	Description
Sitting	0.472	Caregivers for type 2 SMA patients
All patients	0.484	Caregivers for all patients (8 SMA type 1, 60 SMA type 2 and 13 SMA type 3)

Drug/Therapy Utilization

The recommended dosage for nusinersen is 4 loading doses (the first three loading doses administered at 14-day intervals; the 4th loading dose administered 30 days after the 3rd dose) and a maintenance dose administered once every 4 months thereafter.

AVXS-101 is potentially a one-time therapy administered using single intravenous infusion.

Cost Inputs

The costs used in the model include treatment costs, administration/monitoring costs and the costs associated with the health states. Caregiver costs and productivity gains are also included in the modelled costs, when performing analysis with societal perspective. All costs will be inflated to 2018 values using the methods described in the ICER reference case.

Drug Acquisition Costs

Since nusinersen is administered in a hospital setting, we include mark-ups associated with the treatment. We use the average wholesale price (AWP) and apply a 15% discount to the AWP, reflecting the weighted average mark-ups seen for treatments administered in a hospital setting. AVXS-101 currently has no list or net price. We hence assume the upper-end price of AVXS-101 as forecasted by a market analyst. These costs are presented in Table 7.

Table 7. Treatment Cost Inputs

Intervention	Administration	Package size	WAC^ per package	Estimated Real World Price Per Package*	Source
Nusinersen	Intrathecal injection	2.4mg/ml (5ml)	$125,000	$127,500	Redbook 2018[20]; Magellan 2016[21]
AVXS-101	Intravenous infusion	-		$2,000,000	Market analyst estimate[22]

^Wholesale acquisition cost (WAC) as of November 2, 2018

*AWP – 15%, where AWP is $150,000 per package as on November 2, 2018

Administration and Monitoring Costs

All administration, laboratory and monitoring costs associated with the treatment are presented in tables 8 and 9.

Table 8. Costs associated with nusinersen treatment

	Cost	Description	Source
Intrathecal Injection (lumbar puncture into central nervous system)	$82.44	Current Procedural Terminology (CPT) code 96450	Physician fee schedule 2018[23]
Intrathecal injection (drain cerebrospinal fluid)	$86.76	CPT 62272	
MD/Specialist	$52.20	CPT 99213	
Monitor for thrombocytopenia	$5.53	CMS lab fee schedule 85049	
Monitor for renal toxicity	$10.72	CMS lab fee schedule 80069	
Anesthesia for lumbar puncture	$133.13	HCPCS 00635	
Imaging (ultrasound or fluoroscopy – average cost)	$78.66	CPT 77003, 76942	

Table 9. Costs associated with AVXS-101 treatment

	Cost	Description	Source
Single dose intravenous infusion	$74.16 $22.32 per additional hour	CPT 96365 CPT 96366	Physician fee schedule 2018[23]
Anti-AAV9 diagnostic test	$15.89	CPT 86603	
Laboratory monitoring	$10	CPT 80069	
Prednisolone	$0.03*	Oral, 1mg/kg 30-day prescription	Redbook 2018[20]

*Price per mg

Health Care Utilization Costs

The monthly costs associated with the different health states are presented in the table 10 below. They have been sourced from a claims analysis of commercial health plans comprising infantile SMA (n= 23), childhood-onset SMA (n=22) and later onset SMA (n=296) patients, based on the study reported by Shieh et al [24]. The costs of infantile SMA patients are used for 'permanent ventilation' and 'not sitting' health states (Note that we are intending to account for disutility of permanent ventilation, and are reviewing the literature for relevant data on this estimate). The costs of childhood-onset SMA and later onset SMA are used for 'sitting' and 'walking' states, respectively. The costs for non-SMA patients matched to late onset group are used for the 'normal functioning' health state.

Table 10. Background Costs

	Permanent ventilation	Not sitting	Sitting	Walking	Normal functioning
Inpatient hospitalization	$21,863	$21,863	$3,401	$1,116	$185
Outpatient services	$3,341	$3,341	$2,631	$984	$348
Emergency services	$313	$313	$325	$399	$209
Total monthly cost	$25,517	$25,517	$6,357	$2,499	$742

Scenario analyses will also be performed using the cost data from Armstrong et al[25], who report additional annual total health care costs of $112,644 and $30,453 for patients with SMA diagnosed before and after one year of age, respectively.

Scenario analyses will also be performed using the cost data from Lewin et al[26], who report additional annual total health care costs of $121,682 and $20,085 for patients with early onset SMA and for other SMA patients, respectively.

Non-medical costs

The annual non-medical costs associated with the different health states, based on the study reported by Lewin et al[26], are summarized below in table 11. Lewin et al[26] report the costs for early onset SMA and those for other SMA patients. Cost reported for early onset SMA patients will be used for 'permanent ventilation' and 'not sitting' health states, while the costs reported for other SMA patients (i.e. later onset SMA patients) will be used for 'sitting' and 'walking' health states. No costs will be assumed for the patients in 'normal function' health state.

Table 11. Non-medical Costs

	Permanent ventilation	Not sitting	Sitting	Walking	Normal function
Caregiving	$50,542	$50,542	$5,247	$5,247	$0
Moving/ modifying home	$3,685	$3,685	$3,389	$3,389	$0
Moving/ Modifying vehicle	$1,814	$1,814	$2,292	$2,292	$0
Other non-medical costs	$2,106	$2,106	$4,861	$4,861	$0
Total annual cost	$51,665	$51,665	$14,295	$14,295	$0

Productivity

No productivity is assumed for those in 'permanent ventilation' and 'not sitting' states. For those in other states, data from the Lewin group report[26] on educational attainment for SMA patients are combined with data on income by education level in US, to estimate the productivity of the patients.

2.6 Model Outcomes

The model outcomes include life years (LYs) gained, QALYs gained and total costs for each intervention over a lifetime time horizon. Costs and QALYs will also be reported by the health state to understand the contribution of different costs elements. All the costs and QALYs will be reported as discounted values, using a discount rate of 3% per annum.

2.7 Analysis

Cost-effectiveness will be estimated using incremental cost-effectiveness ratios, with incremental analyses comparing the two interventions to BSC, separately, from the health sector and modified societal perspectives in the base case analysis.

Sensitivity Analyses

One-way sensitivity analyses to identify the key drivers of model outcomes. Probabilistic sensitivity analysis (PSA) will be performed by jointly varying all model parameters.

Additionally, we will perform a threshold analysis by systematically altering the price of interventions to estimate the maximum prices that would correspond to given willingness to pay (WTP) thresholds.

Scenario Analyses

In addition to the base case analysis, we plan to conduct the following scenario analyses.

- AVXS-101 will be compared to nusinersen for patients with SMA type 1
- Optimistic/pessimistic scenarios for exploration of motor function milestones
- Assuming utility estimates as reported by multiple sources.
- Assuming health state costs as reported by studies other than that used in the base case analysis.
- Accounting for benefits of achieving head control, rolling, crawling, and standing by varying the utility values in health states to take into account varying quality of life due to achieving these interim milestones
- Hypothetical exploratory analysis comparing AVXS-101 and nusinersen in presymptomatic patients

Model Validation

We will use several approaches to validate the model. First, we will provide preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we will refine data inputs used in the model, as needed. Second, we will vary model input parameters to evaluate face validity of changes in results. We will perform model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we will also share the model with the manufacturers for external verification around the time of publishing the draft report for this review. Finally, we will compare results to other cost-effectiveness models in this therapy area. The outputs from the model will be validated against the trial/study data of the interventions and also any relevant observational datasets.

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