NEW ENGLAND CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL
AN ICER PROGRAM

AVXS-101 and Nusinersen for Spinal Muscular Atrophy: Effectiveness and Value

Research Protocol

October 17th, 2018

Institute for Clinical and Economic Review

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Table of Contents

Background, Objectives, and Research Questions

Background

Spinal muscular atrophy (SMA) is a rare, genetic neuromuscular disease with the most severe cases affecting infants and young children.[1,2] SMA incidence is approximately 1 in 10,000 live births or about 500 new SMA cases per year.[3] The most common cause of SMA is the homozygous deletion or deletion and mutation of the alleles of the survival motor neuron 1 (*SMN1*) gene on chromosome 5q.[4-6] *SMN1* creates SMN protein, a protein essential for motor neuron development. Although the survival motor neuron 2 (*SMN2*) gene also produces SMN protein, only a small amount of the protein it creates is functional. Hence, while the number of *SMN2* copies modulates the severity of SMA, patients without *SMN1* have an insufficient level of SMN protein regardless of the number of *SMN2* copies.[7] This deficiency causes the irreversible degeneration of motor neurons, which leads to progressive muscle weakness and prevents patients from reaching motor milestones or retaining motor functions.[1]

SMA subtypes are related to age of onset and number of motor milestones achieved.[2,8] Type 0 SMA, the most severe subtype, affects individuals before birth and is very rare. Newborns with Type 0 have severe hypotonia (low muscle tone), need respiratory support, and have a life expectancy of minutes to weeks after birth. Type I SMA (infant-onset SMA) represents approximately 60% of all diagnosed SMA cases.[3] These patients typically have two or three copies of *SMN2*, present with symptoms before six months of age, do not reach key motor milestones (e.g., sitting without support), and lose motor functions over time. Pulmonary complications are common, often leading to respiratory support. Patients may die or need permanent respiratory support within two years of life.[3] Approximately 40% of patients diagnosed with SMA have Type II or Type III.[3] Type II SMA presents between 6 to 18 months of age with patients typically having three copies of *SMN2*. These patients cannot walk independently, and most patients survive to adulthood with aggressive supportive care.[3] Type III SMA presents in patients aged 18 months to 18 years, and patients typically have three or four copies of *SMN2*. Patients have a normal life expectancy and can walk independently, although they may lose this ability over time. Type IV SMA, a very rare and the least severe subtype, presents in adults. Adults with Type IV SMA typically retain the ability to walk independently, do not suffer from respiratory issues, and have a normal life expectancy.[2,8]

Patients with SMA may need intensive care and support, especially those with SMA Type I. To maintain mobility and function as long as possible, multidisciplinary, supportive care including respiratory, nutritional, gastrointestinal, orthopedic, and other support is needed.[9-11] Nevertheless, supportive care does not modify disease progression and patients may be entirely dependent on family members and caregivers. The intense care and physical effort involved with caring for a

patient with SMA may cause loss of sleep, stress, anxiety, and emotional distress for caregivers.[12,13] Hence, SMA may affect the health-related quality of life of patients as well as their families and caregivers.

Currently, only one disease-modifying therapy (nusinersen, Spinraza®, Biogen Idec) has been approved to treat SMA.[14] Nusinersen, an antisense oligonucleotide, targets the *SMN2* gene so that it creates more functional SMN protein. It is administered via intrathecal injection with four loading doses (day 0, day 14, day 28, and day 63) and every four months thereafter. Nusinersen has been studied in patients with or likely to develop SMA Types I-III,[15-17] with several studies on-going.[15,18-20] In December 2016, the Food and Drug Administration (FDA) approved nusinersen for the treatment of SMA (any subtype).[14]

A new, systemic gene therapy (AVXS-101, Novartis/AveXis) is currently in development to treat patients with SMA. AVXS-101 uses the adeno-associated virus serotype 9 vector to deliver a copy of the *SMN* gene to replace or correct the defective *SMN1* gene.[21] AVXS-101 is being studied as a one-time, intravenous administration. The FDA granted AVXS-101 a Breakthrough Therapy Designation and Fast Track Designation, with an FDA decision expected in early 2019.[22] The potential use of AVXS-101 has generated interest from clinicians, patients, and their families especially since SMA was recently added to the list of conditions for which to screen all newborns in the US.[23] Nevertheless, uncertainties remain regarding the effectiveness of AVXS-101 and nusinersen compared with supportive care and with each other, and how well the potential cost of these interventions aligns with potential patient benefits. Therefore, stakeholders will benefit from a comprehensive review of the clinical evidence on both drugs and an analysis of their long-term cost-effectiveness and potential budget impact.

Objectives

The scope of this project was previously available for public comment and has been revised upon further discussions and input from stakeholders. In accordance with the revised scope, this project will assess both the comparative clinical effectiveness and economic impacts of AVXS-101 and nusinersen for the treatment of SMA. The assessment aims to systematically evaluate the existing evidence, taking uncertainty into account. To that aim, the assessment is informed by two research components: a systematic review of the existing evidence and an economic evaluation. This document presents the protocol for the systematic review of existing evidence (i.e., the clinical review). See the forthcoming model analysis plan (to be posted October 2018) for details on the proposed methodology and model structure that will be used for the economic evaluation.

Research Questions

To inform our review of the clinical evidence, we have developed the following research questions with input from clinical experts, patients, and patient groups:

1. By type of SMA (types 0-IV) what is the comparative efficacy, safety, and effectiveness, in terms of mortality, permanent invasive ventilatory support, motor function and mobility, respiratory and nutritional support, quality of life, adverse events, and other key outcomes, of:
    - AVXS-101 versus supportive care?
    - Nusinersen versus supportive care?
    - AVXS-101 versus nusinersen?

2. In presymptomatic patients with SMA, what is the comparative efficacy, safety, and effectiveness, in terms of mortality, permanent invasive ventilatory support, motor function and mobility, respiratory and nutritional support, quality of life, adverse events, and other key outcomes, of:
    - AVXS-101 versus supportive care?
    - Nusinersen versus supportive care?
    - AVXS-101 versus nusinersen?

PICOTS Criteria

In line with the above research questions, the following specific criteria have been defined utilizing PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, Setting and Study Design) elements.

Population

The population of focus for the review is infants, children, and adults with SMA. Where data are available, we will look at subpopulations defined by age of onset (including presymptomatic SMA, infant-onset SMA, later-onset SMA), SMA subtype (0-IV), or number of SMN2 copies. It is unlikely that data will be available for all populations and subpopulations, and we will note where gaps in evidence exist.

Interventions

Our review will seek information on AVXS-101 and nusinersen.

Comparators

Where data permit, we intend to compare the agents to each other and to supportive care (with or without sham injections). As noted in the population section above, it is unlikely that all comparisons will be available for all populations and subpopulations, and we will note where gaps in evidence exist.

Outcomes

The outcomes of interest are described below.

Efficacy:

- Mortality
- Permanent invasive ventilatory support
- Motor function, including:
    - Hammersmith Functional Motor Scale-Expanded (HFMSE)
    - Hammersmith Infant Neurological Examination-Section 2 (HINE-2)
    - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)
    - Revised Upper Limb Module (RULM)
    - World Health Organization motor development milestones (sitting without support, standing with assistance, hands-and-knees crawling, walking with assistance, standing along, walking alone)
- Mobility (e.g., 6-Minute Walk Test)
- Bulbar function (e.g., swallowing, speaking)
- Use of respiratory or gastrointestinal support (e.g., gastrointestinal tube)
- Other complications of SMA (e.g., scoliosis)
- Quality of Life (e.g., PedsQoL)

Safety:

- Treatment-related adverse events
    - Injection or infusion site reactions
    - Thrombocytopenia and low platelets
    - Renal toxicity
    - Liver function (e.g., elevated aminotransferase)
    - Complications of lumbar puncture (e.g., back pain, vomiting, headache)
- Serious adverse events
- Adverse events leading to discontinuation

Timing

Evidence on intervention efficacy, safety, and effectiveness will be collected from studies of any duration.

Setting

Evidence from all relevant settings will be considered, including inpatient, outpatient/clinic, office, and home settings.

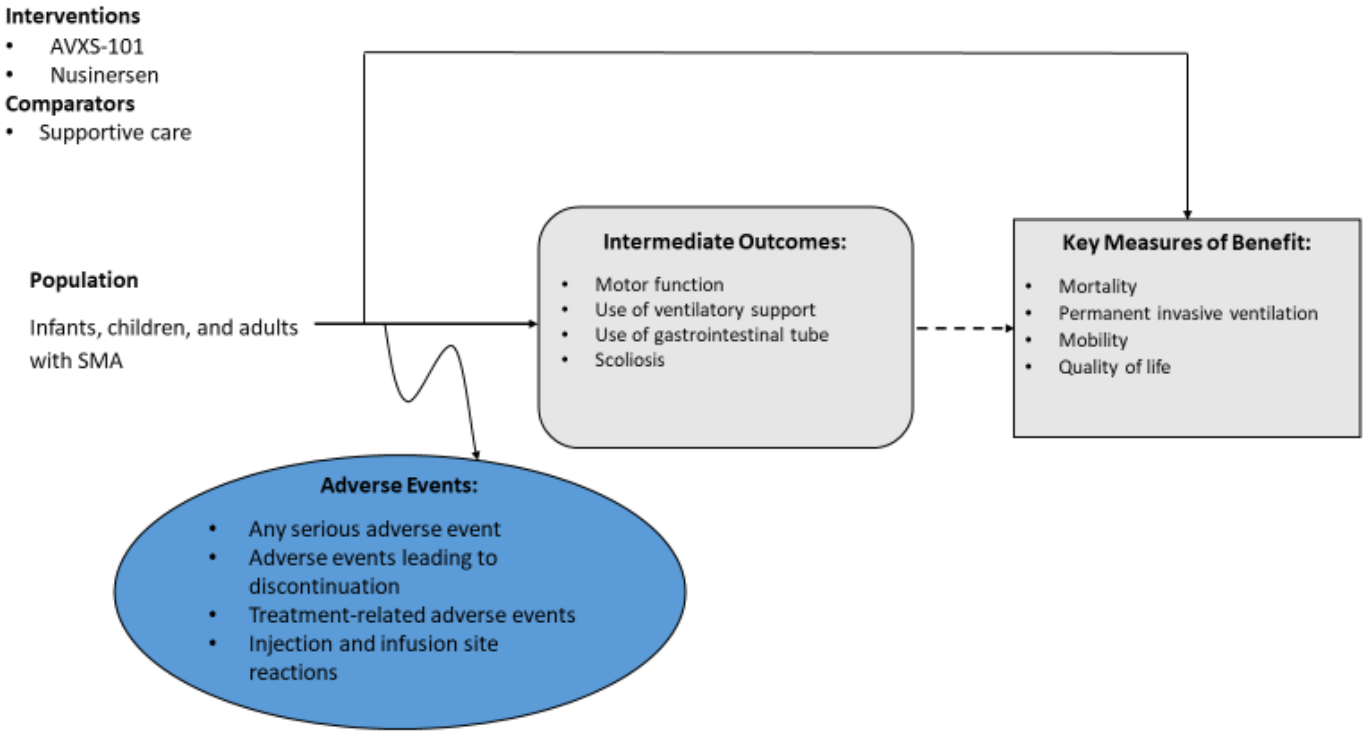
Study design

Randomized controlled trials, non-randomized comparative studies, and single arm-studies with any sample size will be included.

Analytic Framework

The proposed analytic framework for this project is depicted below:

Figure 1. SMA Analytic Framework



The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific clinical or health outcomes. Outcomes are listed in the shaded boxes: those within the rounded boxes are intermediate outcomes (e.g., change in blood pressure), and those within the squared-off boxes are key measures of clinical benefit (e.g., health-related quality of life). The key measures of clinical benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of an action (typically treatment), which are listed within the blue ellipsis.

Evidence Review Methods

Search Methods and Data Sources

Procedures for the systematic literature review assessing the evidence on AVXS-101 and nusinersen for SMA will follow established best methods.[24,25] The results from the review will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[26] The PRISMA guidelines includes 27 checklist items, which are described further in Appendix A.

We will search MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search will be limited to English language studies of human subjects and will exclude articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We will include full-text articles as well as abstracts from conference proceedings identified from the systematic literature search. All search strategies will be generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies include a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Tables 1-2 below.

To supplement the database searches, we will perform a manual check of the reference lists of included trials and reviews and invite key stakeholders to share references germane to the scope of this project. We will also supplement our review of published studies with data from conference proceedings (including CureSMA, AAN, Gene Therapy for Rare Disorders, World Orphan Drug Congress, and American Society of Gene and Cell Therapy), regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Table 1: Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials (using OVID)

1	exp spinal muscular atrophy
2	Werdnig Hoffman.mp.
3	Kugelberg Welander.mp.
4	nusinersen.mp.
5	ISIS$396443.mp.
6	AVXS$101.mp.
7	onasemnogene abeparvovec.mp.
8	OR/1-3
9	OR/4-7
10	8 AND 9
11	(animals not (humans and animals)).sh.
12	10 not 11
13	(addresses or autobiography or bibliography or biography or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video-audio media).pt.
14	12 not 13
15	limit 14 to english language

Table 2. Search strategy of EMBASE SEARCH

#1	'spinal muscular atrophy'
#2	'werdnig hoffmann disease'
#3	'kugelberg welander disease'
#4	#1 or #2 or #3
#5	'onasemnogene abeparvovec'
#6	'avxs 101'
#7	'nusinersen'
#8	'spinraza'
#9	'ISIS 396443'
#10	'antisense oligonucleotide'
#11	'gene therapy'
#12	#5 or #6 or #7 or #8 or #9 OR #10 or #11
#13	#4 AND #12
#14	'animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp
#15	'human'/exp
#16	#14 AND #15
#17	#14 NOT #16
#18	#13 NOT #17
#19	#18 AND [english]/lim
#20	#19 AND ('chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#21	#19 NOT #20

Eligibility Criteria

Studies meeting the PICOTS criteria will be eligible for our review. To be included, studies must assess AVXS-101 or nusinersen (any dose or regimen). For any study that also assesses supportive care, we will accept and use the study's definition of supportive care, noting any potentially clinically relevant differences between studies. We will exclude studies only assessing supportive care (e.g., comparative studies of different support care options or single-arm supportive care studies). Studies comparing different lumbar puncture approaches using nusinersen will be excluded. Studies including SMA patients with any number of SMN2 copies will be included. Case-control studies will be excluded.

Selection of Eligible Studies

Following the literature search and removal of duplicate citations using both online and local software tools, study selection will be accomplished through two levels of screening, at the abstract

and full-text level. Two reviewers will independently screen the titles and abstracts of all publications identified using DistillerSR. No study will be excluded at abstract level screening due to insufficient information. For example, an abstract that does not report an outcome of interest would be accepted for further review in full text.

Citations accepted by either reviewer during abstract-level screening will be retrieved in full-text for further review. The full-text articles will then be independently screened by two reviewers; a third reviewer will work with the initial two reviewers to resolve any disagreements through consensus. Reasons for exclusion will be categorized according to the PICOTS elements during both title/abstract and full-text review.

Data Extraction Strategy

Data will be extracted into forms designed in Microsoft Excel. The basic design and elements of the extraction forms will follow those used for other ICER reports. Elements include a description of patient populations (including type of SMA, pre-symptomatic SMA, ventilation use at baseline, motor function at baseline, age at diagnosis and treatment initiation), sample size, duration of follow-up, funding source, study design features (including randomization, location, frequency of visits), interventions (agent, dosage, frequency, schedules, and routes of administration), supportive therapy allowed and used (including any pharmacologic or non-pharmacologic agent along with frequency and schedules), outcome assessments, results, and risk of bias assessment for each study.

The data extraction will be performed in the following steps:

1. One reviewer will extract information from the full articles, and a second reviewer will validate the extracted data.
2. Extracted data will be reviewed for logic, and a random proportion of data will be validated by a third investigator for additional quality assurance.

Risk of Bias Assessment Criteria

We will use criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials and cohort studies, using the categories "good," "fair," or "poor."[27]

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.

Fair: Any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.

Poor: Any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat or modified intention to treat (e.g., randomized and received at least one dose of study drug) analysis is lacking.

Publication Bias Assessment

Given the emerging nature of the evidence base for these newer treatments, we will scan the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms will include "AVXS-101", "nusinersen", and "Spinraza". We will select studies which would have met our inclusion criteria, and for which no findings have been published. We will review the objectives and methods of these studies to determine whether there may be a biased representation of study results in the published literature.

Evidence Synthesis

The purpose of the evidence synthesis is to estimate the clinical effectiveness of the interventions being compared. The analysis will be based on the data from all relevant studies identified from the systematic review. This section contains two components: (1) a summary of the evidence base and (2) a synthesis of outcome results.

Summary of Evidence Base

The studies will be summarized in the text and in evidence tables of the Evidence Report. This summary is key to understanding the evidence base pertaining to the topic. An evidence table shell is presented in Appendix B. Relevant data include those listed in the data extraction section. Any key differences between the studies in terms of the study design, patient characteristics, interventions (including dosing and frequency), outcomes (including definitions and methods of assessments), and study quality will be noted in the text of the report.

Synthesis of Results

For each outcome of interest, the results of the studies will be presented in the text or tables. Key considerations for interpreting the results will be also be provided. Analyses are expected to be descriptive in nature only as differences in entry criteria, patient populations, outcome assessments, and other factors are likely to preclude formal quantitative direct or indirect assessments of AVXS-101 and nusinersen versus each other or supportive care.

References

1. Mercuri E, Bertini E, Iannaccone ST. Childhood spinal muscular atrophy: controversies and challenges. *Lancet Neurol.* 2012;11(5):443-452.
2. Verhaart IEC, Robertson A, Wilson IJ, et al. Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy - a literature review. *Orphanet J Rare Dis.* 2017;12(1):124.
3. Lally C, Jones C, Farwell W, Reyna SP, Cook SF, Flanders WD. Indirect estimation of the prevalence of spinal muscular atrophy Type I, II, and III in the United States. *Orphanet J Rare Dis.* 2017;12(1):175.
4. Brzustowicz LM, Lehner T, Castilla LH, et al. Genetic mapping of chronic childhood-onset spinal muscular atrophy to chromosome 5q11.2-13.3. *Nature.* 1990;344(6266):540-541.
5. Lefebvre S, Burglen L, Reboullet S, et al. Identification and characterization of a spinal muscular atrophy-determining gene. *Cell.* 1995;80(1):155-165.
6. Wirth B, Herz M, Wetter A, et al. Quantitative analysis of survival motor neuron copies: identification of subtle SMN1 mutations in patients with spinal muscular atrophy, genotype-phenotype correlation, and implications for genetic counseling. *Am J Hum Genet.* 1999;64(5):1340-1356.
7. Butchbach ME. Copy Number Variations in the Survival Motor Neuron Genes: Implications for Spinal Muscular Atrophy and Other Neurodegenerative Diseases. *Front Mol Biosci.* 2016;3:7.
8. Russman BS. Spinal muscular atrophy: clinical classification and disease heterogeneity. *J Child Neurol.* 2007;22(8):946-951.
9. Finkel RS, Mercuri E, Meyer OH, et al. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. *Neuromuscul Disord.* 2018;28(3):197-207.
10. Mercuri E, Finkel RS, Muntoni F, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscul Disord.* 2018;28(2):103-115.
11. Wang CH, Finkel RS, Bertini ES, et al. Consensus statement for standard of care in spinal muscular atrophy. *J Child Neurol.* 2007;22(8):1027-1049.
12. NICE. *Single Technology Appraisal - Nusinersen for treating spinal muscular atrophy [ID1069] - Committee Papers.* National Institute for Health and Care Excellence (NICE);2018.
13. Qian Y, McGraw S, Henne J, Jarecki J, Hobby K, Yeh WS. Understanding the experiences and needs of individuals with Spinal Muscular Atrophy and their parents: a qualitative study. *BMC Neurol.* 2015;15:217.
14. Food and Drug Administration. Spinraza (nusinersen) injection, for intrathecal use [package insert]. 2016.
15. Finkel RS, Chiriboga CA, Vajsar J, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. *Lancet.* 2016;388(10063):3017-3026.
16. Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. *N Engl J Med.* 2017;377(18):1723-1732.
17. Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. *N Engl J Med.* 2018;378(7):625-635.
18. Ascadi G, et al. Safety and Efficacy of Nusinersen in Infants/Children With Spinal Muscular Atrophy (SMA): Part 1 of the Phase 2 EMBRACE Study. Paper presented at: Presented at the 22nd International Annual Congress of the World Muscle Society2017; Saint Malo, France.

19. Castro D, et al. Longer-term Assessment of the Safety and Efficacy of Nusinersen for the Treatment of Infantile-Onset Spinal Muscular Atrophy (SMA): An Interim Analysis of the SHINE Study. Paper presented at: Presented at AAN2018; Los Angeles, CA.
20. De Vivo DC, et al. Nusinersen in Presymptomatic Infants with Spinal Muscular Atrophy: Interim Efficacy and Safety Results from Phase 2 of NURTURE Study. Presented at the CureSMA Conference; 2018; Dallas, TX.
21. Mendell JR, Al-Zaidy S, Shell R, et al. Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy. *N Engl J Med.* 2017;377(18):1713-1722.
22. Novartis AG. Q2 2018 Results: Investor Presentation. 2018; https://www.novartis.com/investors.
23. Department of Health and Human Services. Recommended Uniform Screening Panel (July 2018). 2018; https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html. Accessed 8/22/2018.
24. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med.* 1997;126(5):376-380.
25. Higgins JP, Green S. *Cochrane Collaboration Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011].* The Cochrane Collaboration and John Wiley & Sons Ltd; 2008.
26. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *International journal of surgery (London, England).* 2010;8(5):336-341.
27. Agency for Healthcare Research and Quality. *U.S. Preventive Services Task Force Procedure Manual.* 2008.
28. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *Bmj.* 2009;339:b2700.

Appendix A. PRISMA Checklist

The checklist below is drawn from Moher et al. 2009.[26] Additional explanation of each item can be found in Liberati et al. 2009.[28]

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

doi:10.1371/journal.pmed.1000097.t001

Appendix B. Data Extraction Summary Table Shells

Table B1. Baseline Characteristics Extraction Table Shell

	Study 1		Study 2		Study 3		Study 4	
Baseline Characteristics	**Arm A**	**Arm B**	**Arm A**	**Arm B**				
Mean age (range) – months								
Female sex – no. (%)								
Mean age at symptom onset (range) – months								
Mean age at genetic diagnosis (range) – months								
Mean score on CHOP-INTEND scale (SD/range)								
Use of ventilator support – no. (%)								
Use of nutritional support[b] – no. (%)								

Table B2. Key Outcomes Extraction Table Shell

	Study 1		Study 2		Study 3		Study 4	
Outcome	**Arm A**	**Arm B**	**Arm A**	**Arm B**				
Deaths – no. (%)								
Permanent invasive ventilation – no. (%)								
Event-free survival – no. (%)								
Mean score on CHOP-INTEND scale (SD/range)								
Mean HFMSE score								
Use of ventilator support – no. (%)								
Use of nutritional support[b] – no. (%)								

Table B3. Harms Extraction Table Shell

	Study 1		Study 2		Study 3		Study 4	
Outcome	Arm A	Arm B	Arm A	Arm B				
Treatment-related adverse events								
Injection or infusion site reactions								
Thrombocytopenia and low platelets								
Renal toxicity								
Liver function (e.g., elevated aminotransferase)								
Lumbar puncture-related AEs								
Back pain								
Vomiting								
Headache								
Serious AEs								
AEs leading to discontinuation								