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Systematic Literature Review

Cost-Effectiveness of Technologies for the Treatment of Spinal Muscular Atrophy: A Systematic Review of Economic Studies

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RESUMO

Objetivo: Este estudo tem como objetivo coletar sistematicamente dados sobre análises de custo-efetividade que avaliam tecnologias para tratamento de AME tipo I e II e avaliar suas recomendações.

Métodos: Foi realizada uma busca eletrônica estruturada em quatro bases de dados. Adicionalmente, foi realizada uma busca manual complementar. Foram selecionados estudos econômicos completos que avaliaram nusinersen, risdiplam, onasemnogene abeparvovec (OA) e a melhor terapia de suporte (BST) na perspectiva do sistema de saúde. As razões de custo-efetividade incrementais foram comparados com vários limiares para a análise. A revisão foi registrada a priori no PROSPERO (CRD42022365391).

Resultados: Vinte estudos foram incluídos nas análises. Todos foram publicados entre 2017 e 2022 e representam as recomendações em oito países. A maioria dos estudos adotou modelos de Markov de 5, 6 ou 10 estados. Alguns autores participaram de vários estudos. Foram avaliadas quatro tecnologias: BST (N=14), nusinersen (N=19), risdiplam (N=5) e OA (N=9). OA, risdiplam e nusinersen foram considerados ineficientes em comparação ao BST. Risdiplam e OA foram geralmente considerados custo-efetivos quando comparados ao nusinersen. Como o nusinersen é um medicamento não custo-efetivo, nenhuma recomendação pode ser derivada deste resultado. Risdiplam e OA foram comparados em dois estudos que apresentaram resultados opostos.

Conclusão: Nusinersen, risdiplam e OA estão sendo adotados mundialmente como tratamento para AME. Apesar disso, as análises farmacoeconômicas mostram que as tecnologias não são custo-efetivas em comparação com o BST. A falta de estudos controlados para o risdiplam e a OA dificulta quaisquer conclusões sobre a sua comparação face a face.

Palavras-Chave: Análise de custo-benefício, Atrofia Muscula Espinhal, Nusinersen, Risdiplam, Onasemnogene Abeparvovec.

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ABSTRACT

Objectives: This study aims to systematically collect data on cost-effectiveness analyses that assess technologies to treat type I and II spinal muscular atrophy and evaluate their recommendations.

Methods: A structured electronic search was conducted in 4 databases. Additionally, a complementary manual search was conducted. Complete economic studies that evaluated nusinersen, risdiplam, onasemnogene abeparvovec (OA), and the best support therapy (BST) from the health system's perspective were selected. The incremental cost-effectiveness ratios were compared with various thresholds for the analysis. The review was registered a priori in PROSPERO (CRD42022365391).

Results: Twenty studies were included in the analyses. They were all published between 2017 and 2022 and represent the recommendations in 8 countries. Most studies adopted 5, 6, or 10-state Markov models. Some authors took part in multiple studies. Four technologies were evaluated: BST (N = 14), nusinersen (N = 19), risdiplam (N = 5), and OA (N = 9). OA, risdiplam, and nusinersen were considered inefficient compared with the BST. Risdiplam and OA were generally regarded as cost-effective when compared with nusinersen. Because nusinersen is not a cost-effective drug, no recommendation can be derived from this result. Risdiplam and OA were compared in 2 studies that presented opposite results.

Conclusions: Nusinersen, risdiplam, and OA are being adopted worldwide as a treatment for spinal muscular atrophy. Despite that, the pharmacoeconomic analyses show that the technologies are not cost-effective compared with the BST. The lack of controlled studies for risdiplam and OA hamper any conclusions about their face-to-face comparison.

Keywords: cost-benefit analysis, muscular atrophy, onasemnogene abeparvovec, nusinersen, risdiplam, spinal.

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Introduction

Spinal muscular atrophy (SMA) is a rare, progressive, and incapacitating neuromuscular disorder characterized by atrophy and weakness of the skeletal, bulbar, and respiratory muscles.[1-5] The disease is most commonly caused by homozygous deletion or loss-of-function mutations in the SMN1 (survival motor neuron 1) gene.[5] The 5q-related SMA is autosomal recessive and represents about 95% of the cases.[2,4-7] The incidence of the disease is estimated to be between 4 and 10 cases per 100 000 live births and the prevalence of the carrier status is 1 per 54 individuals.[2,4] The severity of the disease is inversely associated with the number of copies of the SMN2 gene, which produces small amounts of a less functional protein.[7] Most patients have SMA type 0 (prenatal onset) and type 1 (infantile onset), which have worse prognoses. Death usually happens by the second year of life.[2,7] Type 2 SMA, an intermediate form of the disease, accounts for 20% of the cases. Some motor milestones are achieved in this case, and the life expectancy is uncertain.[2]

The treatment of the disease depends on new pharmacological entities and support treatment. The best support therapy (BST) is based on nutrition, respiratory assistance, and treatment of the complications of muscular weakness.[2] The pharmacological options registered in the last few years are nusinersen (2016), risdiplam (2020), and onasemnogene abeparvovec (OA, 2019). All 3 drugs enhance the SMN protein expression.[5,7-9] Nusinersen requires quarterly injections throughout the patient's lifetime.[5,8] Risdiplam requires daily drug doses throughout the patient's lifetime.[1,3] OA is an innovative gene therapy designed to deliver a functional copy of human SMN with a single-dose scheme.[7] It should be taken in the first months of life because the effectiveness of the technology seems to be better when the patients are treated close to the diagnosis of the disease.[9-11]

Nusinersen, risdiplam, and OA were studied in 8 trials: CHERISH[5] and ENDAR[8] for nusinersen; FIREFISH[1,3] and SUNFISH[12,13] for risdiplam; and START,[9,14] STR1VE,[7] STR1VE-EU,[10] and SPR1NT[15] for OA. Nusinersen was considered superior to sham for early- and later-onset patients,[5,8] whereas risdiplam was superior to placebo for later-onset patients.[12,13] Risdiplam and OA for early-onset patients were only assessed through single-arm studies. These trials suggest that the individuals on the targeted therapies have better results than a historic cohort regarding event-free survival, various scales, or overall survival.[1,3,9,10,14,15] The safety profiles of all 3 drugs are acceptable. Still, safety issues are more present in studies with risdiplam and OA than nusinersen, although there is no face-to-face comparison. Some indirect studies tried to compare the different technologies, but they do not preclude the need for a direct comparison.[16-18]

Nusinersen, risdiplam, and OA can be considered effective for SMA patients. However, they have entered the market at very high prices. The Veteran Affairs reported Federal Supply Schedule fees for these drugs are: US$133 237.25 for nusinersen 12 mg/5 mL vial, US$11 588.95 for risdiplam 0.75 mg/ML 80 mL oral suspension, and US$2 155 753.77 for OA.[19] These price levels raise questions about the feasibility of their subsidy by public health systems. Despite that, many countries chose to list them.[20-30] The disease's severity, the technologies' potential efficacy, and the social context help explain these decisions. Nonetheless, the opportunity costs of these technologies might be very relevant to the unidentified individuals who bear them, especially in low- and middle-income countries. OA, for example, has been considered the most expensive drug in the world.[31-35] This study aims to systematically collect data on cost-effectiveness analyses that assess these technologies and evaluate their recommendations. This knowledge is paramount to support decision-making worldwide.

Methods

This systematic aims to answer the question: Which technology is more cost-effective for treating type I and II SMA worldwide? The research question in Population, Intervention, Comparator, Outcomes, and Study designs format is available in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2024.02.002. This report follows the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[36] (Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2024.02.002). The review was registered a priori in PROSPERO (CRD42022365391).

Search Strategies

A structured electronic search was conducted in Medline (via PubMed), Embase, Lilacs/BRISA/RedTESA (via *Biblioteca Virtual em Saúde*), and the Center for Reviews and Dissemination. Various descriptors and related terms were used, such as "Cost-Benefit Analysis," "Cost-Effectiveness Analysis," "Cost-Utility Analysis," "Economic evaluation," "Muscular Atrophy," "Spinal," "risdiplam," "nusinersen," and "onasemnogene abeparvovec" (Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2024.02.002). A complementary search in Google Scholar, field journals, ProQuest, and conference proceedings were also performed. The references were exported to EndNote X7 for duplicate removal and then imported into the online app Rayyan QCRI[37] for selection.

Study Selection and Data Collection

The selection process was conducted in 2 phases. Phase I was a screening of titles and abstracts. The full texts were assessed in phase II. Complete economic analyses that compared type I or II SMA treatment strategies were included. The studies had to adopt the health system's perspective or equivalent. Cost-minimization analyses were excluded. Only outcomes associated with the patient were considered (ie, results that combine benefits for patients, family members, and caregivers were excluded). No restrictions on date, language, or country were imposed.

A spreadsheet was designed for data collection. This spreadsheet contains information on the country of origin, study design, perspective, currency, time horizon, cycle length, number of health states, discount rate, and sponsor (Appendix 4 in

Supplemental Materials found at https://doi.org/10.1016/j.vhri.2024.02.002). Additional information was collected in open forms (Appendix 5 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2024.02.002). At least 2 independent researchers conducted all phases, and the diversions were resolved by consensus.[38]

Data Analysis

Initially, the general and methodological characteristics of the studies were described (eg, country, year of the publication, SMA type, time horizon, model type, and discount rate). Following this description, a qualitative analysis was used to examine the studies' results, the authors' recommendations, and their association with the study sponsor. Also, a network graph of the relationship between the researcher's institution and the selected studies was built using R.[39] Finally, because there is no widely accepted consensus on the cost-effectiveness threshold (λ), the incremental cost-effectiveness ratio (ICER) of each study was compared with different values for λ. For this analysis, the recommendation of the original manuscript was disregarded. A wide range of λ values was chosen to represent various decision contexts.[40] These benchmarks were (1) the explicit threshold in the country of origin (if available); (2) the 50 000 US dollar (USD)/quality-adjusted life-years (QALYs) precedent approach threshold[41-43]; (3) the updated 100 000 USD/QALY precedent threshold[40,43]; the updated 150 000 USD/QALY precedent threshold[40,43]; (4) the opportunity costs threshold (κ) estimated for the country of origin[44-47]; (5) the 3 gross domestic product (GDP) per capita/QALY or disability-adjusted life-years threshold[40,48-50]; (6) 2 GDP per capita/QALY; and (7) 1 GDP per capita/QALY. A higher threshold value of 500 000 USD/QALY was also tested because of the rare nature of the SMA disease. These higher thresholds for rare, severe conditions have been suggested in the last few years.[51,52]

All ICERs were converted into purchase power parity (PPP)-USD of the year of the study using the PPP conversion rate calculated by the International Monetary Fund. The conversion was performed in the online Campbell & Cochrane Economics Methods Group-Evidence for Policy & Practice Information-Center Cost Converter tool.[53] The base year of the monetary value should be reported in the articles. In the cases it was not presented, the year of submission or publication was considered in this order. When the ICER was not available, it was calculated by the authors.

Quality of the Included Studies

There is no widely accepted instrument to evaluate the quality of complete economic studies.

Results

The electronic and complementary searches returned 134 records. After duplicate removal, 108 were screened. In phase I, 81 studies were excluded. Twenty-seven full texts were retrieved and analyzed in phase II. Seven were excluded by perspective, repetition, and study type. In the final analysis, 20 studies were included (Appendix 6 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2024.02.002). The included and excluded studies lists are available in Appendices 7 and 8 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2024.02.002.

Characteristics of the Included Studies

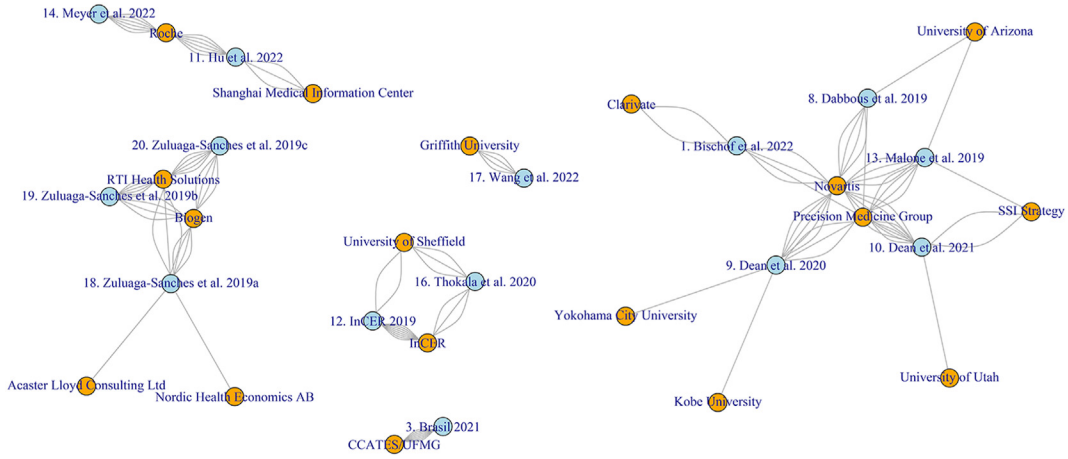
All articles were published between 2017 and 2022. The articles of most studies (65%) were published in only 2 years, 2019 and 2022. Eight countries were represented: the USA (N = 9), Brazil (N = 4), Australia (N = 1), Sweden (N = 1), Japan (N = 1), Ireland (N = 1), China (N = 1), and Canada (N = 2). Nusinersen was compared with the BST in 14 studies (19 comparisons). The second most common comparison was OA vs nusinersen (N = 8). Most records were reports from health technology assessment (HTA) agencies (N = 8) and conference abstracts (N = 7). Research articles were only 5. Seventeen studies reported the cost-effectiveness of the drugs for early-onset patients, and 7 considered late-onset patients. The pharmaceutical companies sponsored 9 studies: Biogen (N = 3), Novartis (N = 5), and Roche (N = 1). One study did not report any funding, and government and research-promoting organizations or HTA agencies supported the other 10 (Appendix 9 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2024.02.002).

Most studies adopted a 5, 6, or 10-state Markov model. The most common health states were "Within normal range of development," "not sitting," "sitting," "standing," "walking," "permanent ventilation," and "death." Discount rates varied between 1.5% (N = 2) and 5% (N = 7). The cycle lengths ranged from monthly (N = 6) to yearly (N = 2), and the time horizons ranged from 10 years (N = 3) to a lifetime (N = 12). All studies considered the QALY as the outcome measure (Appendix 10 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2024.02.002). Data for comparing different drugs were primarily derived from matching-adjusted indirect comparisons [54,55] or naive comparisons. All studies suffered from difficulties in extrapolating the data from some months to many years. The extrapolations were mainly conducted using historical cohorts, probability distributions, and the Cox proportional hazards assumption. Some studies evaluated more than 1 subgroup of patients, but there is a higher interest in early-onset SMA.

Some authors took part in multiple studies (Appendix 11 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2024.02.002). In the 17 records that reported the authors, there were 73 individuals. Most of them only appeared once in the sample (61%), 25% appeared twice, and 8% appeared thrice. Two authors (Douglas Sproule and Douglas Feltner) were listed 4 times. Omar Dabbous (N = 5) and Rebecca Dean (N = 5) were the authors listed in more studies. Partnerships between different institutions were common. For instance, Dean et al,[56,57] Malone et al,[58] and Zuluaga-Sanchez et al[59] had authors from 4 institutions, and Bischof et al[60] and Dabbous et al[61] from 3 institutions (Appendix 12 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2024.02.002).

Figure 1 shows a network graph of the institutions responsible for each study. The image shows 7 isolated clusters. Three were associated with sponsored research (from Biogen, Roche, and Novartis), 3 were related to HTA agencies (*Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde* and Institute for Clinical and Economic Review [InCER]), and 1 seems to be an independent analysis.[62] In the largest of these clusters, it can be seen that the articles of Dean et al,[56,57] Malone et al,[58] Bischof et al,[60] and Dabbous et al[61] are connected by authors from the same institutions. Novartis and Precision Medicine Group are at the center of the network. Authors from the University of Arizona, University of Utah, Clarivate, Yokohama University, Kobe University, and SSI Strategy participated in some of these studies. These institutions can be seen on the outside of the cluster image. Authors from 2 institutions connect the 3 studies from Zuluaga-Sanchez et al[59,63,64]: Biogen and RTI Solutions. One of the studies also has authors from Acaster Lloyd Consulting Ltd and Nordic Health Economics AB. Roche was only associated with 2 studies.[65,66] One of these, from China, also has authors from the Shanghai Medical Information Center. InCER and the University of

Figure 1. Network graph linking studies and author institutions.



Sheffield are associated with the InCER-related articles.[67,68] Their model might be the most influential in the group, given the importance of InCER as an HTA agency. One of the reports from Brazil[21] was made by *Centro Colaborador do SUS para Avaliação de Tecnologias e Excelência em Saúde*, an HTA-supporting institution. The other 2 did not report the affiliations of the authors.[22,23] Four studies did not inform the individual authors or their affiliations.[20,69-71]

Qualitative Synthesis of Drugs Comparisons

Four technologies were evaluated in the 20 articles as the intervention or comparator: BST (N = 14), nusinersen (N = 19), risdiplam (N = 5), and OA (N = 9). In total, these articles provided 39 comparisons. Nusinersen was compared with BST in 19 scenarios. Eleven of these considered early-onset or type I patients. Only 1 study,[20] from Brazil, had an ICER below the highest threshold (500 000 USD/QALY). Eight studies compared nusinersen with BST for late-onset or type II/III patients. In this case, 2 comparisons demonstrated an ICER < 500 000 USD/QALY, 1 from Brazil[21] and the other from Sweden.[59] OA and risdiplam were also compared with BST. Two HTA reports from Brazil compared risdiplam and BST: 1 for early-onset patients[23] and the other for late-onset patients.[22] Both observed high values for the ICER (2 306 120 USD/QALY and 34 376 889 USD/QALY, respectively). Four records compared OA and BST for early-onset SMA. Two were HTA reports,[69,71] and 2 were complete articles.[57,62] Wang et al[62] evaluated the use of OA in Australia and found an ICER of 1 255 011 USD/QALY. Canadian Agency for Drugs and Technologies in Health (CADTH),[71] InCER,[67] and Dean et al[57] observed less-extreme values for the ICER (277 023, 243 000, and 161 648 USD/QALY, respectively). However, the authors did not suggest the technology was cost-effective in their studies (Table 1).

Risdiplam was compared with nusinersen in 4 records.[22,23,65,66] Two (1 from the USA and the other from China) found risdiplam to be dominant over nusinersen.[65,66] The other 2, from Brazil, found very high ICER values (1 442 206[23] and 23 994 735 USD/QALY[22]). Only 2 studies evaluated risdiplam vs OA.[60,66] Both studies evaluated the cost-effectiveness of the drugs in the USA and were published in 2022. However, their results were the opposite. Bischof et al[60] found OA to be dominant over risdiplam and Meyer et al[66] found risdiplam to be dominant over OA. Eight comparisons between OA and nusinersen were available.[56-58,61,62,66,67,71] Six of them found OA to be dominant over nusinersen.[56-58,61,66,71] These evaluations were conducted considering the USA (N = 4), Japan (N = 1), and Canada (N = 1). Wang et al[62] found an ICER of 1 238 288 for Australia, and the InCER[67] found an ICER of 139 000 for the USA. Therefore, Wang et al[62] concluded that the technology was not cost-effective in their analysis, and the InCER suggested that it could be considered cost-effective depending on the regulator (Table 1).

Table 2 summarizes the recommendations made by the authors stratified by comparison and funding. Initially, it can be noticed none of the technologies can be considered cost-effective against BST, independently of the sponsor. Risdiplam was deemed superior to nusinersen by funded and unfunded studies. OA was generally regarded as superior to nusinersen as well, except for 1 nonfunded study that favored nusinersen. Lastly, OA and risdiplam were compared in 2 studies: 1 was funded by Novartis and the other by Roche. Both studies were published in 2022 and evaluated the drug for the USA. The results of the study funded by Novartis favored OA,[60] and the study financed by Roche selected risdiplam.[66] It can be noticed that studies funded by Novartis generally favor OA, except when it is compared with BST. The same is true for Roche and risdiplam. Biogen did not sponsor any cost-effectiveness study comparing nusinersen with risdiplam or OA.

Threshold Analysis

Table 3 compares all ICERs with the previously described threshold levels. The 19 comparisons between nusinersen and BST generally favored BST at all threshold levels except for 3 reference [20,21,59]; 2 included late-onset patients,[21,59] and 1 evaluated early-onset individuals.[20] The drug was only considered cost-effective at the 500 000 USD/QALY threshold in these records. Risdiplam was only compared with BST by 2 references from Brazil[22,23]; 1 in early-onset patients and 1 in late-onset patients. Risdiplam was not considered cost-effective at any threshold level. There were 4 comparisons between OA and BST. Wang et al[62] did not consider OA to be cost-effective at any threshold level for type I patients in Australia. InCER[67] and Canadian Agency for Drugs and Technologies in Health[71] only found OA efficient at the 500 000 USD/QALY threshold. Dean et al[57] considered the technology to be cost-effective at 500 000 USD/QALY and 3 GDP per capita/QALY.

Table 1. Results of the studies in PPP-USD.

Study SMA type	Country currency/ year*	Interventions	Costs	Effectiveness	ICER†	ICER‡ (PPP-USD)	1 GDP per capita (Int$)§	Unit of effectiveness
Nusinersen vs BST (early-onset) – 11 comparisons								
Brasil,[20] 2019	Brazil	Nusinersen	2 978 861.29	1.79	1 023 351	494 611	15 358	QALY
Early-onset	BRL/2019	BST	256 127.38	−0.74				
Brasil,[22] 2022a – 3	Brazil	Nusinersen	2 166 935.03	0.56	7 237 221	3 276 243	16 056‖	QALY
Early-onset	BRL/2022	BST	21.483.26	0.26				
Canadian Agency for Drugs and Technologies in Health[69]	Canada	Nusinersen	3 534 854	3.919	665 570	551 425	49 299	QALY
Type I	CAD/2019	BST	339 683	–0.881				
CADTH,[71] 2021 – 3	Canada	Nusinersen	3 938 147	4.54	878 879¶	728 755	69 287	QALY
Early-onset	CAD/2021	BST	132 600	0.21				
Dean et al,[57] 2021 – 3	USA	Nusinersen	4 602 692	2.85	1 553 519	1 553 519	69 287	QALY
Type I	USD/2021	BST	1 961 710	1.15				
InCER 2019 – 1[67]	USA	Nusinersen	3 884 000	3.24	1 112 000	1 112 000	59 915	QALY
Early-onset	USD/2017	BST	789 000	0.46				
NCPE, 2017[72]	Ireland	Nusinersen	NA	NA	501 069	602 971	77 749	QALY
Early-onset	EUR/2017	BST	NA	NA				
Thokala et al,[68] 2020	USA	Nusinersen	3 884 000	3.24	1 112 000	1 112 000	59 914	QALY
Early-onset	USD/2017	BST	789 000	0.46				
Wang et al,[62] 2022 – 2	Australia	Nusinersen	2 592 526	0.602	2 772 798	1 924 218	55 807‖	QALY
Type I	AUD/2022	BST	923 335	0.301				
Zuluaga-Sanchez et al,[59] 2019a	Sweden	Nusinersen	22 970 891	3.65	5 664 875	640 967	53 521	QALY
Early-onset	SEK/2018	BST	1 513 607	−0.20				
Zuluaga-Sanchez et al,[63] 2019b	USA	Nusinersen	NA	2.05	>500 000	>500 000	65 095	QALY
Early-onset	USD/2019	BST		0.41				
Nusinersen vs BST (late-onset) – 8 comparisons								
Brasil,[21] 2021	Brazil	Nusinersen	3 930 025	5.74	811 739	375 457	16 056	QALY
Late-onset	BRL/2021	BST	28 186	0.93				
Brasil,[23] 2022b – 3	Brazil	Nusinersen	9 551 218	9.73	96 352 206	43 618 020	16 056‖	QALY
Late-onset	BRL/2022	BST	168 094	9.63				
Canadian Agency for Drugs and Technologies in Health[69]	Canada	Nusinersen	8 336 271	23.278	2 075 435	1 719 499	49 299	QALY
Type 2	CAD/2019	BST	708 620	19.602				
Canadian Agency for Drugs and Technologies in Health[69]	Canada	Nusinersen	5 554 707	12.053	2 855 818	2 366 046	49 299	QALY
Type 3	CAD/2019	BST	1 091 307	10.490				
InCER 2019[67]	USA	Nusinersen	9 148 000	12.28	8 156 000	8 156 000	59 915	QALY
Late-onset	USD/2017	BST	1 442 000	11.34				
NCPE, 2017[72]	Ireland	Nusinersen	NA	NA	2 107 108	2 535 629	77 749	QALY
Late-onset	EUR/2017	BST	NA	NA				
Zuluaga-Sanchez et al,[59] 2019a	Sweden	Nusinersen	64 095 327	9.25	3 985 640	450 966	53 522	QALY
Late-onset	SEK/2018	BST	25 175 193	− 0.29				
Zuluaga-Sanchez et al,[64] 2019c	USA	Nusinersen	NA	13.89	>500 000	>500 000	65 095	QALY
Late-onset	USD/2019	BST		12.71				
Risdiplam vs BST (early-onset) – 1 comparison								
Brasil,[22] 2022a – 2	Brazil	Risdiplam	3 227 472.67	0.89	5 094 220	2 306 120	16 056‖	QALY
Early-onset	BRL/2022	BST	21 483.26	0.26				
Risdiplam vs BST (late-onset) – 1 comparison								
Brasil,[23] 2022b – 2	Brazil	Risdiplam	14 145 685	9.81	75 938 549	34 376 889	16 056‖	QALY
Late-onset	BRL/2022	BST	168 094	9.63				
OA vs BST (early-onset) – 4 comparisons								
CADTH,[71] 2021 – 2	Canada	OA	3 266 544 (sponsor)	10.89 (sponsor)	293 521 (sponsor)	243 384 (sponsor)	69 287	QALY

continued on next page

Table 1. Continued

Study SMA type	Country currency/ year*	Interventions	Costs	Effectiveness	ICER†	ICER‡ (PPP-USD)	1 GDP per capita (Int$)§	Unit of effectiveness
Early-onset	CAD/2021	BST	3 249 578 (CADTH)	9.883 (CADTH)	334 090 (CADTH)	277 023 (CADTH)		
			132 600 (sponsor)	0.21 (sponsor)				
Dean et al,[57] 2021 – 2	USA	OA	3 930 879	13.33	161 648	161 648	69 287	QALY
Type I	USD/2021	BST	1 961 710	1.15				
InCER 2019 – 2[67]	USA	OA	3 657 000	12.23	243 000	243 000	59 915	QALY
Early-onset	USD/2017	BST	789 000	0.46				
Wang et al,[62] 2022 – 1	Australia	OA	5 034 806	2.574	1 808 471	1 255 011	55 807‖	QALY
Type I	AUD/2022	BST	923 335	0.301				
Risdiplam vs Nusinersen (early-onset) – 3 comparisons								
Brasil,[22] 2022a – 1	Brazil	Risdiplam	3 227 472.67	0.89	3 185 834	1 442 206	16 056‖	QALY
Early-onset	BRL/2022	Nusinersen	2 166 935.03	0.56				
Hu et al,[65] 2022	China	Risdiplam	−207 486 (incremental)	1.41 (incremental)	Dominance	Dominance	19 338‖	QALY
Type I	CNY/2022	Nusinersen						
Meyer et al,[66] 2022 – 2	USA	Risdiplam	–1 303 561	0.44	Dominance	Dominance	69 287‖	QALY
Type I	USD/2022	Nusinersen	(incremental)	(incremental)				
Risdiplam vs Nusinersen (late-onset) – 1 comparison								
Brasil,[23] 2022b – 1	Brazil	Risdiplam	14 145 685	9.81	53 004 369	23 994 735	16 056‖	QALY
Late-onset	BRL/2022	Nusinersen	9 551 218	9.73				
OA vs Nusinersen (early-onset) – 8 comparisons								
CADTH,[71] 2021 – 1	Canada	OA	3 266 544	10.89	Dominance	Dominance	69 287	QALY
Early-onset	CAD/2021	Nusinersen	3 938 147	4.54				
Dabbous et al,[61] 2019	USA	OA	3.657M	12.23	Dominance	Dominance	65 094	QALY
Type I	USD/2019	Nusinersen	3.884M	3.24				
Dean et al,[56] 2020	Japan	OA	266M	14.5	Dominance	Dominance	42 100	QALY
Type I	JPY/2020	Nusinersen	330M	2.5				
Dean et al,[57] 2021 – 1	USA	OA	3 930 879	13.33	Dominance	Dominance	69 287	QALY
Type I	USD/2021	Nusinersen	4 602 692	2.85				
InCER 2019 – 3[67]	USA	OA	5 301 000	13.46	139 000	139 000	59 915	QALY
Early-onset	USD/2017	Nusinersen	3 884 000	3.24				
Malone et al,[58] 2019	USA	OA	4.2–6.6M	15.65	Dominance	Dominance	65 094	QALY
Type I	USD/2019	Nusinersen	6.3M	5.29				
Meyer et al,[66] 2022 – 3	USA	OA	-675.392	0.36	Dominance	Dominance	69 287‖	QALY
Type I	USD/2022	Nusinersen	(incremental)	(incremental)				
Wang et al,[62] 2022 – 3	Australia	OA	5 034 806	2.574	1 238 288	859 325	55 807‖	QALY
Type I	AUD/2022	Nusinersen	2 592 526	0.602				
OA vs Risdiplam (early-onset) – 2 comparisons								
Bischof et al,[60] 2022	USA	Risdiplam	10.4M	5.0	Dominance	Dominance	69 287	QALY
Type I	USD/2021	OA	2.125M	10.4				
Meyer et al,[66] 2022 – 1	USA	Risdiplam	–628 169	0.08	Dominance	Dominance	69 287‖	QALY
Type I	USD/2022	OA	(incremental)	(incremental)				

BST indicates best support therapy; CADTH, Canadian Agency for Drugs and Technologies in Health; CCEMG-EPPI, Campbell & Cochrane Economics Methods Group-Evidence for Policy & Practice Information; GDP, gross domestic product; ICER, incremental cost-effectiveness ratio; NA, not applicable; NCPE, National Centre for Pharmacoeconomics; OA, onasemnogene abeparvovec; PPP, purchase power parity; QALY, quality-adjusted life-year; SMA, spinal muscular atrophy; USA, United States of America; USD, US dollar.

*If the base year of the monetary value was not presented in the study, the year of submission or publication of the study was considered in that order.

†The ICER informed by the authors was used preferentially. When not available for comparison, it was calculated using the formula (C1-C2)/(E1-E2), where C = Cost and E = Effectiveness.

‡Values converted by applying the purchase power parity calculated by the International Monetary Fund using the CCEMG-EPPI-Centre Cost Converter tool[53] to PPP-USD of the base year of the study.

§Data from the World Bank for the base year of study. Available at: https://data.worldbank.org/indicator/NY.GDP.PCAP.PP.CD. Accessed on: 07/21/2021.

‖Data for 2021.

¶Our estimate.

Table 2. Study recommendations made by the authors and study funding.

Comparison/Recommended drug	Number of studies by the sponsor			
	Novartis (onasemnogene abeparvovec)	Roche (risdiplam)	Biogen (nusinersen)	Other/none
Nusinersen vs BST				
Nusinersen				
BST	1		4	10+4*
Risdiplam vs BST				
Risdiplam				
BST				2*
Onasemnogene abeparvovec vs BST				
Onasemnogene abeparvovec				
BST	1			3
Risdiplam vs Nusinersen				
Risdiplam		1		3
Nusinersen				
Onasemnogene abeparvovec vs Nusinersen				
Onasemnogene abeparvovec	4	1		2
Nusinersen				1
Onasemnogene abeparvovec vs Risdiplam				
Onasemnogene abeparvovec	1	1		
Risdiplam				

BST indicates best support therapy; HTA, health technology assessment; QALY, quality-adjusted life-year; USD, US dollar.
*These results are from Brazil's HTA agency reports. No threshold was suggested in the studies. Therefore, we assume anything over 150 000 USD/QALY is excessive. This threshold is the highest indicated by the authors in the sample.

Risdiplam was compared with nusinersen 4 times for the USA (N = 1), China (N = 1), and Brazil (N = 2): 1 for late-onset patients[22] and 3 for early-onset patients.[23,65,66] Risdiplam was considered dominant over nusinersen in 2 studies.[65,66] In the other 2, from Brazil, it was not cost-effective at any threshold value.[22,23] There are only 2 comparisons between OA and risdiplam.[60,66] As mentioned before, they are from the USA, were published in 2022, and have opposite results. Lastly, there are 8 comparisons between OA and nusinersen. Six studies found OA to be dominant over nusinersen.[56-58,61,66,71] InCER[67] found an ICER of 139 000 USD/QALY for early-onset patients in the USA. In this case, OA would be cost-effective at 150 000 USD/QALY, 500 000 USD/QALY, and 3 GDP per capita/QALY. Wang et al[62] found an ICER of 859 325 USD/QALY for early-onset patients in Australia. In their study, OA was not cost-effective at any threshold level.

Discussion

Our systematic review suggests that all 3 drugs—OA, risdiplam, and nusinersen—are not cost-effective compared with the BST. The efficacy and safety of the technologies are acceptable, especially for early-onset patients (Appendix 13 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2024.02.002).[1,3,5,7-10,12-15] Despite that, the high prices of the drugs seem to have made the treatment too costly. Nusinersen was the first of these drugs to enter the market and the first to be listed by many healthcare systems for treating SMA. As soon as the drug was incorporated, it became the obvious choice of comparator for the other entrants. Nusinersen was compared with BST much more frequently than risdiplam or OA (19 times vs 2 vs 4, respectively). Risdiplam and OA were most commonly compared with nusinersen (4 and 8 times, respectively). Risdiplam and OA were generally considered cost-effective when compared with nusinersen. However, the problem with this comparison is that nusinersen is not a cost-effective drug. Proving that a drug is cost-effective compared with another one that is not does not lead to an adequate and precise recommendation.

Twelve studies adopted the healthcare system's perspective, 7 reported the third-party payer's perspective, and 1 did not explicitly say this information. The third-party payer perspective is similar to the healthcare system's; therefore, it was accepted. However, this review did not include the modified societal perspective.[57] This perspective incorporates the caregivers' loss of quality of life in the analysis. Understandably, the caregiver also loses the quality of life when a child with SMA is in the family. This assertion is true not only for SMA but also for mental health disorders, cancers, Down Syndrome, multiple sclerosis, amyotrophic lateral sclerosis, cystic fibrosis, and many others. Despite that, economic models typically include only outcomes related to the patient in the effectiveness analysis. The understanding is that the results evaluated by the health system should reflect the patient's well-being—not the caregivers.' Considering the outcomes for caregivers, family members, and other parties might generate distortions, such as compounding the utilities to more than 1 and less than 0 in usual situations; eg, someone could inadvertently affirm that a drug produces more than 1 QALY a year because it improves the quality of life of the patient in 0.6 utils and the caregiver in 0.5 or that a disease is worse than death because it provokes the loss of 0.6 utils by the patient and 0.5 by the caregiver. It seems like an attempt to make drugs seem more cost-effective than they really are.

Some authors and institutions took part in multiple studies. This observation is relevant because it is associated with the lack of variability between studies. The methods applied by the same research groups are probably very similar. The studies of Dabbous

Table 3. Comparison of the results with cost-effectiveness thresholds in PPP-USD in the base year of the study.

Study	Country	Comparison	ICER (PPP-USD)	λ*	50 000 USD	150 000 USD	500 000 USD	κ†	3 GDP per capita	2 GDP per capita	1 GDP per capita
Bischof et al,[60] 2022	USA	Risdiplam	Dominance	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Type I	USD/2021	OA		150 000				24 283-40 112	207 861	138 574	69 287
Brasil,[20] 2019	Brazil	Nusinersen	494 611	NA	No	No	Yes	No	No	No	No
Early-onset	BRL/2019	BST						3210-10 122	46 074	30 716	15 358
Brasil,[21] 2021	Brazil	Nusinersen	375 457	NA	No	No	Yes	No	No	No	No
Late-onset	BRL/2021	BST						3210-10 122	48 168	32 112	16 056
Brasil,[22] 2022a – 1	Brazil	Risdiplam	1 442 206	NA	No	No	No	No	No	No	No
Early-onset	BRL/2022	Nusinersen						3210-10 122	48 168	32 112	16 056
Brasil,[22] 2022a – 2	Brazil	Risdiplam	2 306 120	NA	No	No	No	No	No	No	No
Early-onset	BRL/2022	BST						3210-10 122	48 168	32 112	16 056
Brasil,[22] 2022a – 3	Brazil	Nusinersen	3 276 243	NA	No	No	No	No	No	No	No
Early-onset	BRL/2022	BST						3210-10 122	48 168	32 112	16 056
Brasil,[23] 2022b – 1	Brazil	Risdiplam	23 994 735	NA	No	No	No	No	No	No	No
Late-onset	BRL/2022	Nusinersen						3210-10 122	48 168	32 112	16 056
Brasil,[23] 2022b – 2	Brazil	Risdiplam	34 376 889	NA	No	No	No	No	No	No	No
Late-onset	BRL/2022	BST						3210-10 122	48 168	32 112	16 056
Brasil,[23] 2022b – 3	Brazil	Nusinersen	43 618 020	NA	No	No	No	No	No	No	No
Late-onset	BRL/2022	BST						3210-10 122	48 168	32 112	16 056
Canadian Agency for Drugs and Technologies in Health[69]	Canada	Nusinersen	551 425	No	No	No	No	No	No	No	No
Type I	CAD/2019	BST		41 425				21 051-26 564	147 897	98 598	49 299
Canadian Agency for Drugs and Technologies in Health[69]	Canada	Nusinersen	1 719 499	No	No	No	No	No	No	No	No
Type 2	CAD/2019	BST		41 425				21 051-26 564	147 897	98 598	49 299
Canadian Agency for Drugs and Technologies in Health[69]	Canada	Nusinersen	2 366 046	No	No	No	No	No	No	No	No
Type 3	CAD/2019	BST		41 425				21 051-26 564	147 897	98 598	49 299
CADTH,[71] 2021 – 1	Canada	OA	Dominance	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Early-onset	CAD/2021	Nusinersen		41 459				21 051-26 564	207 861	138 574	69 287
CADTH,[71] 2021 – 2	Canada	OA	243 384 (sponsor)	No	No	No	Yes	No	No	No	No
Early-onset	CAD/2021	BST	277 023 (CADTH)	41 459				21 051-26 564	207 861	138 574	69 287
CADTH,[71] 2021 – 3	Canada	Nusinersen	728 755	No	No	No	No	No	No	No	No
Early-onset	CAD/2021	BST		41 459				21 051-26 564	207 861	138 574	69 287
Dabbous et al,[61] 2019	USA	OA	Dominance	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Type I	USD/2019	Nusinersen		150 000				24 283-40 112	195 282	130 188	65 094
Dean et al,[56] 2020	Japan	OA	Dominance	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Type I	JPY/2020	Nusinersen		150 000				24 283-40 112	126 300	84 200	42 100
Dean et al,[57] 2021 – 1	USA	OA	Dominance	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

continued on next page

Table 3. Continued

Study	Country	Comparison	ICER (PPP-USD)	λ*	50 000 USD	150 000 USD	500 000 USD	κ†	3 GDP per capita	2 GDP per capita	1 GDP per capita
Type I	USD/2021	Nusinersen		150 000				24 283-40 112	207 861	138 574	69 287
Dean et al,[57] 2021 – 2	USA	OA	161 648	No	No	No	Yes	No	Yes	No	No
Type I	USD/2021	BST		150 000				24 283-40 112	207 861	138 574	69 287
Dean et al,[57] 2021 – 3	USA	Nusinersen	1 553 519	No	No	No	No	No	No	No	No
Type I	USD/2021	BST		150 000				24 283-40 112	207 861	138 574	69 287
Hu et al,[65] 2022	China	Risdiplam	Dominance	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Type I	CNY/2022	Nusinersen		58 014‡				2013-7957	58 014	38 676	19 338[5]
InCER 2019 – 1[67]	USA	Nusinersen	1 112 000	No	No	No	No	No	No	No	No
Early-onset	USD/2017	BST		150 000				24 283-40 112	179 745	119 830	59 915
InCER 2019 – 2[67]	USA	OA	243 000	No	No	No	Yes	No	No	No	No
Early-onset	USD/2017	BST		150 000				24 283-40 112	179 745	119 830	59 915
InCER 2019 – 3[67]	USA	OA	139 000	Yes	No	No	Yes	No	Yes	No	No
Early-onset	USD/2017	Nusinersen		150 000				24 283-40 112	179 745	119 830	59 915
InCER 2019[67]	USA	Nusinersen	8 156 000	No	No	No	No	No	No	No	No
Late-onset	USD/2017	BST		150 000				24 283-40 112	179 745	119 830	59 915
Malone et al,[58] 2019	USA	OA	Dominance	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Type I	USD/2019	Nusinersen		150 000				24 283-40 112	195 285	130 190	65 095
Meyer et al,[66] 2022 – 1	USA	Risdiplam	Dominance	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Type I	USD/2022	OA		150 000				24 283-40 112	207 861	138 574	69 287
Meyer et al,[66] 2022 – 2	USA	Risdiplam	Dominance	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Type I	USD/2022	Nusinersen		150 000				24 283-40 112	207 861	138 574	69 287
Meyer et al,[66] 2022 – 3	USA	OA	Dominance	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Type I	USD/2022	Nusinersen		150 000				24 283-40 112	207 861	138 574	69 287
NCPE, 2017[72]	Ireland	Nusinersen	602 971	No	No	No	No	No	No	No	No
Early-onset	EUR/2017	BST		54 152				21 071-26 634	233 247	155 498	77 749
NCPE, 2017[72]	Ireland	Nusinersen	2 535 629	No	No	No	No	No	No	No	No
Late-onset	EUR/2017	BST		54 152				21 071-26 634	233 247	155 498	77 749
Thokala et al,[68] 2020	USA	Nusinersen	1 112 000	No	No	No	No	No	No	No	No
Early-onset	USD/2017	BST		150 000				24 283-40 112	179 745	119 830	59 915
Wang et al,[62] 2022 – 1	Australia	OA	1 255 011	NA	No	No	No	No	No	No	No
Type I	AUD/2022	BST						21 153-26 938	167 421	111 614	55 807
Wang et al,[62] 2022 – 2	Australia	Nusinersen	1 924 218	NA	No	No	No	No	No	No	No
Type I	AUD/2022	BST						21 153-26 938	167 421	111 614	55 807
Wang et al,[62] 2022 – 3	Australia	OA	859 325	NA	No	No	No	No	No	No	No

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Table 3. Continued

Study	Country	Comparison	ICER (PPP-USD)	λ*	50 000 USD	150 000 USD	500 000 USD	κ†	3 GDP per capita	2 GDP per capita	1 GDP per capita
Type I	AUD/2022	Nusinersen						21 153-26 938	167 421	111 614	55 807
Zuluaga-Sanchez et al,[59] 2019a	Sweden	Nusinersen	640 967	No	No	No	No	No	No	No	No
Early-onset	SEK/2018	BST		79 203 – 138 040				21 148-26 917	160 563	107 042	53 521
Zuluaga-Sanchez et al,[59] 2019a	Sweden	Nusinersen	450 966	No	No	No	Yes	No	No	No	No
Late-onset	SEK/2018	BST		79 203 – 138 040				21 148-26 917	160 563	107 042	53 522
Zuluaga-Sanchez et al,[63] 2019b	USA	Nusinersen	>500 000	No	No	No	No	No	No	No	No
Early-onset	USD/2019	BST		150 000				24 283-40 112	195 285	130 190	65 095
Zuluaga-Sanchez et al,[64] 2019c	USA	Nusinersen	>500 000	No	No	No	No	No	No	No	No
Late-onset	USD/2019	BST		150 000				24 283-40 112	195 285	130 190	65 095

BST indicates best support therapy; GDP, gross domestic product; ICER, incremental cost-effectiveness ratio; InCER, Institute for Clinical and Economic Review; NA, not applicable; NCPE, National Centre for Pharmacoeconomics; OA, onasemnogene abeparvovec; PPP, purchase power parity; USA, United States of America; USD, US dollar.
Ochalek et al,[73] 2020.
Santos et al,[40] 2018.
Woods et al,[47] 2016.
*Results taken from implicit or explicit thresholds discussed by Santos et al.[40]
†The values were taken from Woods et al[47] and has not been adjusted. Opportunity costs thresholds are not usually adjusted by inflation.
‡Value taken from Ochalek et al[73] (2020).

et al,[61] Malone et al,[58] Dean et al,[56,57] and Bischof et al[60] are interconnected by the authors and institutions. It is worth mentioning that authors from Thokala et al[68] are also responsible for the model from the InCER.[67] The results from Thokala et al[68] are the same as InCER's for the comparison between nusinersen and BST.[67] Because InCER is a very reputable institution, this model is influential. Dean et al[57] updated their research group's model considering the publication of InCER's report.[67]

There might be funding bias in the analyses. This effect is apparent in the comparisons of OA vs nusinersen and OA vs risdiplam. The studies sponsored by Novartis[56-58,60,61] tend to present much more favorable results for OA than other studies.[62,67] Anyway, opposite results for analyses conducted for the same country and the same period should not be possible.[60,66] The impact of sponsorship on the results of studies is not unprecedented.[74,75] Lexchin et al[76] showed that studies funded by the industry are not different in quality from other studies. Despite that, they produce more favorable estimates for the sponsor's drug. Santos et al[75] and Heres et al[74] found that about 90% of the publications funded by pharmaceutical companies favor their new technologies. In the case of economic evaluations, the assumptions, model structures, and study parameters must be assessed to determine if they have been chosen to privilege a specific technology. One apparent problem in the present analysis is the efficacy and safety of the drugs. The sample sizes and follow-up times of the studies are short. Also, the data for comparing agents were primarily derived from matching-adjusted indirect comparisons[54,55] or naive comparisons. Methods that compare study results without a proper anchoring group are insufficient to convince an analyst of the magnitude of the relative effect between treatment strategies. Indirect unanchored methods match individual patient data from 1 study to the aggregated data from another study to provide a comparison.[77] It has been demonstrated that the individual patient data used might influence the analysis result.[78-80]

The pharmaceutical companies understand that these drugs are too expensive for consumers. They aim to convince decision makers to approve their funding inside public health systems or private insurance claims. These decision makers are limited by the constraints of their budget and the opportunity costs of their choices. Every health system in the world has scarce resources—ie, policy makers cannot invest in all desired policies at the same time and obtain exceptional results. Opportunity cost is the benefit of the best alternative course of action not taken after a decision. The standard cost-effectiveness model is grounded on opportunity costs.[44,47,81-84] When decision makers invest in a new, more expensive technology, resources must be displaced from other system parts to fund it. The benefits gained from this technology must be higher than the benefits forgone by the displacement of resources. That is, net health benefits must be positive. Otherwise, the health system is paying for the technology more than it is worth.[82,85-87] After the drug is developed, its cost-effectiveness can only be influenced by its price. Therefore, these drugs require a considerable price reduction to be considered efficient in most countries.

Companies seem confident that decision makers value equity (ie, equality of health state[88]) more than efficiency. The λ (cost-effectiveness threshold) level that guarantees that consumers do not have negative net benefits is κ (opportunity costs value for λ). It can be observed in Table 3 that this threshold is the lowest among the suggested values. Some authors have even suggested exceptional threshold levels for severe rare diseases, such as SMA. England's Highly Specialized Medicine program increases λ when the technology is used to treat small populations and rare

conditions. The value suggested was 100 000 GBP/QALY for technologies that add more than 10 QALYs over the patient's lifetime. This value can be proportionately increased up to 300 000 GBP/QALY (431 654.68 PPP-USD/QALY) depending on the number of QALYs added until the limit of 30 QALY.[51] Garrison et al[52] suggest that InCER is willing to accept up to a threshold of 500 000 USD/QALY for an effective treatment for ultra-rare diseases. The permissiveness of these thresholds is unprecedented.[40]

There are some limitations worth mentioning. (1) Most studies did not report the base year of their analysis; therefore, the moment of submission or publication of the record had to be used to conduct further investigations. The error derived from this approximation should have little relevance to the results. (2) We assumed it would be clearly stated when an author used a modified social perspective. Some reports were unclear in this matter.[56,57,61] (3) The methods used to extrapolate the data constitute a fragility of all the models. The drugs can be considered efficacious, but the magnitude of effect and the relationship between different drugs is uncertain because of the lack of a control group in risdiplam and OA trials. STR1VE, STR1VE-EU, STR1VE, FIREFISH, and SUNFISH were mainly conducted after 2016.[3,7,10,12] Nusinersen was already available at the moment of recruitment. The protocols could have been amended to incorporate it as the comparator. It is unclear why this was not done. (4) There is a problem in extrapolating short-term data to very long time horizons. The statistical treatment is not enough to guarantee the trustworthiness of the results. (5) Many reports did not categorize patients into types of SMA but into early- or late-onset SMA. Early-onset SMA is type 0 and type I, and late-onset SMA includes type II and III. Initially, our review intended to focus on type I and II patients. Nevertheless, these studies that categorize the patients in early- and late-onset were accepted, given that type I and II were the most prevalent types of SMA in the data used to parameterize the models. (6) The previously discussed possibility of funding bias diminishes confidence in the results. A brief description of all included studies can be found in Appendix 14-16 in Supplemental Materials (https://doi.org/10.1016/j.vhri.2024.02.002).

Nusinersen, risdiplam, and OA are being adopted worldwide as a treatment for SMA. Despite that, the pharmacoeconomic analyses show that the technologies are not cost-effective compared with the BST. The lack of controlled studies for risdiplam and OA hamper any conclusions about their face-to-face efficiency. More and better-controlled studies are necessary to improve confidence in the treatment and comparative analyses.

Author Disclosures

Links to the disclosure forms provided by the authors are available here.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.vhri.2024.02.002.

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