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REVIEW

Systematic Literature Review of Clinical and Economic Evidence for Spinal Muscular Atrophy

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ABSTRACT

Introduction: The recent advent of disease-modifying therapies (DMTs) has dramatically changed the treatment landscape of spinal muscular atrophy (SMA), and the multifaceted impact of this advancement has not been assessed thoroughly in the growing body of literature. We sought to summarize the literature on the natural history of SMA and the impact of SMA DMTs, including health-related quality of life (HRQOL) and utilities, clinical efficacy and safety, and economic impact.

Methods: Systematic literature reviews were conducted following PRISMA guidelines with no inclusive dates. Relevant studies were identified by searching full-text databases on November 12–13, 2020, including MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and EconLit, conference proceedings, health technology assessment databases, and clinical trial registries. All searches used a combination of MeSH and key terms. Studies were screened according to criteria based upon population, intervention, outcomes, and study design structure.

Results: Findings from 17, 23, 32, and 42 studies were included for the evaluation of natural history of SMA, HRQOL and utilities, clinical efficacy and safety, and economic impact of DMTs, respectively. Currently available data indicate that untreated SMA is associated with considerable humanistic and economic burden, with estimates of costs vary-

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ing by treatment. While a variety of interventions have been evaluated in SMA clinical trials, quantitative synthesis of safety and efficacy findings was not feasible because of inconsistencies in reported outcomes. Data assessing impacts of DMTs on HRQOL were also lacking. ***Conclusions***: Overall, this systematic literature review highlights a clear need for up-to-date and methodologically rigorous clinical, HRQOL, and economic data to support unbiased assessments of the relative clinical and economic effectiveness of SMA treatments. More research is required to extend our understanding of the burden of SMA on HRQOL utility assessments and the impact of new DMTs on HRQOL and utilities for patients with SMA.

Keywords: Disease-modifying therapies; Economic burden; Gene therapy; Health-related quality of life; Humanistic burden; Natural history; Nusinersen; Onasemnogene abeparvovec; Spinal muscular atrophy; Systematic literature review

Key Summary Points

Why carry out this study?

The advent of disease-modifying therapies has transformed the treatment landscape for spinal muscular atrophy, which is reflected by the large volume of recent literature.

We conducted a systematic literature review to summarize this material, focusing on the natural history of spinal muscular atrophy and the impact of disease-modifying therapies, including clinical efficacy and safety, health-related quality of life, and economic impact.

What was learned from the study?

Our literature review indicates substantial methodological heterogeneity between studies in the large volume of recent literature on spinal muscular atrophy and disease-modifying therapies for spinal muscular atrophy in particular. We conclude that opportunities for synthesis (and thus ability to reach overarching conclusions on the relative efficacies and safety results of different interventions) are limited.

The variety of interventions evaluated in clinical trials reflects a changing therapeutic landscape in which disease-modifying therapies have recently been developed and approved.

Overall, this review highlights a clear need for up-to-date and methodologically rigorous clinical, health-related quality of life, and economic data to support unbiased assessments of the relative clinical and economic effectiveness of spinal muscular atrophy treatments.

INTRODUCTION

Spinal muscular atrophy (SMA) is a rare autosomal recessive disease that is caused by biallelic mutations in the *survival motor neuron 1* (*SMN1*) gene [1, 2]. The most severe forms of SMA are characterized by motor neuron degeneration and progressive loss of muscle function that culminate in death or permanent ventilation early in childhood [3].

Before the development of disease-modifying therapies (DMTs), prognoses for patients with SMA were changing because of advances in nutritional and respiratory care, physiotherapy, and strategies to maintain independent living. While some improvements were achieved for even the most severely impacted patients, no clinical evidence confirmed that these strategies altered any neuropathologic process or neuromuscular function (i.e., mechanism of disease) [4].

Moreover, although several different compounds were investigated in randomized controlled trials (RCTs), including treatments intended to increase muscle function and strength (e.g., hyperacetylation agents, anabolics, thyrotropin-releasing hormone, growth hormone, neuroprotective agents such as gabapentin, riluzole, and olesoxime), all produced negative results for their respective primary endpoints, and none were approved [5]. However, with the advent of DMTs (e.g., nusinersen, risdiplam, and onasemnogene abeparvovec), the prognosis for patients with SMA has significantly improved. Prior to these discoveries, SMA was the leading genetic cause of infant mortality [1, 6]. Adherence to the recommendations put forth in the 2007 Consensus Statement for the Standard of Care in Spinal Muscular Atrophy, which includes early assessments of respiratory, feeding, and nutritional needs, may help reduce the severity of SMA and improve health-related quality of life (HRQOL) for patients with SMA [7].

Nusinersen is an antisense oligonucleotide that modifies pre-messenger RNA splicing of the *survival motor neuron 2* (*SMN2*) gene to promote increased production of full-length, functional SMN protein. Treatment is initiated with four loading doses followed by maintenance dosage once every 4 months [8, 9]. In a sham-controlled RCT (ENDEAR; NCT02193074) [10], patients with nusinersen-treated SMA type 1 experienced a significantly greater likelihood of event-free survival ($P = 0.005$) and motor milestone response (51% vs. 0) compared with the control group [10]. Overall survival was significantly greater in the nusinersen group versus the control group ($P = 0.004$).

Onasemnogene abeparvovec is a gene replacement therapy that delivers a functional human *SMN* transgene to motor neurons via one-time intravenous infusion [11]. In the Phase I START study (NCT02122952; $n = 15$), treatment of symptomatic SMA with onasemnogene abeparvovec resulted in significant improvements in survival, motor milestones, and function without the need for permanent ventilation [12]. STR1VE-US (NCT03306277) [13], a completed Phase III study, demonstrated that the favorable risk-benefit profile first observed in START [12] was confirmed for a larger group of patients ($n = 22$ vs. $n = 15$). In STR1VE-US, 59% of patients receiving onasemnogene abeparvovec achieved functional independent sitting for 30 s or longer at the 18-months-of-age study visit (vs. 0 in the untreated cohort; $P < 0.0001$) and 91% survived free from permanent ventilation at age 14 months (vs. 26% in the untreated cohort; $P < 0.0001$).

Risdiplam is a *SMN2* splicing modifier designed to treat patients with SMA that is caused by mutations in chromosome 5q that lead to SMN protein deficiency [14]. In FIREFISH, 41% (7/17) of infants treated with the therapeutic dosage achieved the ability to sit without support for at least 5 s as measured by the Bayley Scales of Infant and Toddler Development Third Edition (BSID-III) [15]. In addition, 90% (19/21) of infants were alive without permanent ventilation at 12 months of treatment and reached 15 months of age or older [16]. In SUNFISH, children and adults treated with risdiplam experienced a clinically meaningful and statistically significant improvement in motor function at 12 months (1.55 point mean difference; $P = 0.0156$) compared with placebo (1.36 points [95% CI 0.61, 2.11]; –0.19

points [95% CI –1.22, 0.84], respectively), as measured by a change from baseline in the Motor Function Measure-32 total score [17].

Based upon these trial results, nusinersen has been approved for use in the United States, Europe, Canada, Japan, and several other countries in Asia and the Middle East. Onasemnogene abeparvovec has been approved for use in the United States, Europe, Japan, and many other countries in South America and Asia. Risdiplam has been approved in the United States and European Union [14, 18]. Nusinersen and onasemnogene abeparvovec are also recommended by the National Institute for Health and Care Excellence (NICE) in the United Kingdom [19].

While the advent of DMTs has clearly and dramatically improved prognoses for patients with SMA, their full impact is unquestionably multifactorial and not completely understood. Therefore, we conducted systematic literature reviews (SLRs) to summarize and provide a landscape synthesis of the current published literature on the natural history of SMA, the HRQOL and utilities, the impact of recent DMTs (including efficacy and safety), and the economic burden of SMA.

METHODS

Literature reviews were performed on November 12–13, 2020, and were designed, completed, and reported following PRISMA guidelines [20]. Full-text studies were identified by searching the following databases: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and EconLit. Inclusive dates were not used for this SLR. Full methodology for searches for all four SLRs can be found in the Supplementary Material.

Study Selection and Eligibility Criteria

Study eligibility criteria were defined based on the population, interventions, comparators, outcomes, and study design structure outlined in Tables 1, 2, 3, and 4, which guided the

Table 1 Eligibility criteria for review of natural history studies

Criteria	Description
Population	Type 1, type 2, and type 3; presymptomatic and symptomatic SMA
Interventions	No intervention or BSC (natural history)
Comparators	No intervention or BSC (natural history)
Outcomes	Overall survival
	Event-free survival
	Evaluation of motor function (e.g., CHOP INTEND)
	Achievement or deterioration of motor milestones
	Ventilation support
	Nutritional support
Study design	Prospective cohort studies with ≥12 months of follow-up
	Randomized controlled trials[a]

BSC best supportive care, *CHOP INTEND* Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders scale, *SMA* spinal muscular atrophy

[a]The searches for the natural history review did not contain terms for randomized controlled trials but did contain terms for observational study designs. Randomized controlled trials that were identified from the searches for the separate clinical efficacy and safety systematic literature review were included in the natural history review as "additional materials" if they had a no intervention or BSC arm

Table 2 Eligibility criteria for review of HRQOL and utilities

Criteria	Description
Population	Type 1, type 2, and type 3; presymptomatic and symptomatic SMA
Interventions	Any of the following interventions used in the treatment of SMA:
	Nusinersen
	Onasemnogene abeparvovec
	Branaplam
	CK-2127107
	RO7034067/RG7916
	RO6885247
	Olesoxime
	Proactive ventilator use and insufflator/exsufflator use ("cough assist")
	4-Aminopyridine
	Anti-cholinesterase therapy/pyridostigmine bromide
	Celecoxib
	Hydroxyurea
	Leuprolide and testosterone
	Pyridostigmine
	Riluzole
	Sodium phenylbutyrate
	Somatotropin
	Valproic acid
	Valproic acid and levocarnitine
	Air stacking technique
	Assisted Standing Treatment Program
	Exercise
	Palliation
	Whole body vibration therapy
Comparators	No restrictions

Table 2 continued

Criteria	Description
Outcomes	*HRQOL measures:*
	EQ-5D
	PedsQL
	For SMA types 2 and 3, other relevant HRQOL scales are also included
	Caregiver HRQOL scales are also included
	Health state utility values:
	HUI-2
	HUI-3S
	SF-6D
	SF-36
Study design	Randomized controlled trials or single-arm or non-randomized controlled trials, including subsequent trial publications reporting on HRQOL outcomes/utilities
	Economic evaluations reporting utility values
	Mapping algorithms
	Observational studies reporting HRQOL/utility
	Literature reviews summarizing results of primary research studies[a]

EQ-5D EuroQoL 5 Dimension, *HRQOL* health-related quality of life, *HUI* health utility index, *PedsQL* Pediatric Quality of Life Inventory, *SF-36* Short-Form survey with 36 items, *SF-6D* Short-Form Six-Dimension, *SMA* spinal muscular atrophy

[a]Literature reviews that involve some type of methodology for study identification and study selection will be of interest. This will include systematic literature reviews, structured literature reviews, scoping reviews, and landscape reviews. Narrative reviews that did not involve study identification via databases and are primarily summarizing an author's viewpoints are not of interest

identification and selection of studies related to each of the four SLRs, respectively. Only prospective studies with at least 12 months of follow-up were included in our analysis. Further information regarding the review and data selection process can be found in the Supplementary Material. Two reviewers (RG, AK), working independently, reviewed all materials identified by the search according to the selection criteria, with the exception of outcome criteria, which were only applied during the screening of full-text publications. All studies identified as eligible during abstract screening were then screened at a full-text stage by the same two reviewers. The full-text studies identified at this stage were included for the data extraction. Following reconciliation between the two investigators, a third reviewer (YZ) was added to reach consensus for any remaining discrepancies. The process of study identification and selection for each SLR is summarized with PRISMA flow diagrams (Figs. 1, 2, 3, 4) [20]. For RCTs with a placebo arm, data from the placebo arm were included in the review of natural history.

The endpoints considered in the included studies are all objective clinical outcomes, including survival outcomes, motor

Table 3 Eligibility criteria for review of clinical efficacy and safety

Criteria	Description
Population	Type 1, type 2, and type 3; presymptomatic and symptomatic SMA
Interventions	Any of the following interventions used in the treatment of SMA:
	Nusinersen
	Onasemnogene abeparvovec
	Branaplam
	CK-2127107
	RO7034067/RG7916
	RO6885247
	Olesoxime
	Proactive ventilator use and insufflator/exsufflator use ("cough assist")
	4-Aminopyridine
	Anti-cholinesterase therapy/pyridostigmine bromide
	Celecoxib
	Hydroxyurea
	Leuprolide and testosterone
	Pyridostigmine
	Riluzole
	Sodium phenylbutyrate
	Somatotropin
	Valproic acid
	Valproic acid and levocarnitine
	Air stacking technique
	Assisted Standing Treatment Program
	Exercise
	Palliation
	Whole body vibration therapy
Comparators	No restrictions

Table 3 continued

Criteria	Description	
Outcomes	SMA type 1	SMA types 2 and 3
	Efficacy outcomes:	*Efficacy outcomes:*
	Mortality (time-to-event)	Disability score (e.g., Hammersmith Functional Motor Score, Upper Limb Module, Hammersmith Functional Motor Scale Expanded, Motor Function Measure, Gross Motor Function Measure), where possible transformed to Modified Rankin Scale
	Event-free survival	
	Achievement of motor milestones	Muscle strength (e.g., dynamometry, isometric strength testing, manual muscle testing), where possible transformed to Medical Research Council Sum score
	The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders response	Ambulatory status
	Time from treatment onset until full-time ventilation (≥16 out of 24 h, regardless of ventilation type)	Forced vital capacity
	Safety outcomes:	*Safety outcomes:*
	Any adverse events	Any adverse events
	Treatment-related adverse events	Treatment-related adverse events
Study design	Randomized controlled trials	
	Single-arm or non-randomized controlled trials	

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functionality, and ventilation support, which are not likely to be exposed to bias from the placebo effect. The double-blind study design also minimizes the risk of the placebo effect.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Systematic Literature Review of Natural History

Study Selection and Overview

Figure 1 presents the PRISMA flow diagram of the study selection process for the search to identify RCTs and prospective cohort studies of interest for the SLR of the natural history of SMA types 1, 2, and 3. Of the 17 natural history studies identified by this SLR, one (ENDEAR [10, 21–25]) was an RCT, and those remaining were either prospective or longitudinal cohort studies. The ENDEAR RCT was conducted internationally across centers in Europe, North America, and Asia Pacific. Three other studies were conducted internationally in North America and Europe. Among the included studies, three were conducted at multiple centers in North America, six at multiple centers in Europe, three at single centers in the United States, Chile, and Spain, and one in The Netherlands. Of these observational studies, only one (NeuroNEXT [26]) was comparative, assessing individuals with SMA type 1 versus matched healthy control infants. Each study had a planned follow-up duration of ≥12 months. A summary of study

Table 4 Eligibility criteria for review of economic burden

Criteria	Description
Population	Type 1, type 2, and type 3; presymptomatic and symptomatic SMA
Interventions	Any of the following interventions used in the treatment of SMA:
	Nusinersen
	Onasemnogene abeparvovec
	Branaplam
	CK-2127107
	RO7034067/RG7916
	RO6885247
	Olesoxime
	Proactive ventilator use and insufflator/exsufflator use ("cough assist")
	4-Aminopyridine
	Anti-cholinesterase therapy/pyridostigmine bromide
	Celecoxib
	Hydroxyurea
	Leuprolide and testosterone
	Pyridostigmine
	Riluzole
	Sodium phenylbutyrate
	Somatotropin
	Valproic acid
	Valproic acid and levocarnitine
	Air stacking technique
	Assisted Standing Treatment Program
	Exercise
	Palliation
	Whole body vibration therapy
Comparators	No restrictions
Outcomes	Resource utilization
	Direct costs
	Indirect costs
	Costs combined with clinical endpoints (e.g., clinical outcomes, utilities, life-years, quality-adjusted life-years, resource use, burden of illness)

Table 4 continued

Criteria	Description
Study design	Include:
	Primary research studies, including:
	Observational studies (e.g., controlled before-and-after studies, interrupted-time series studies, historically controlled studies, prospective and retrospective cohort studies, time and motion studies, case–control studies, cross-sectional studies, controlled and uncontrolled longitudinal studies)
	Randomized controlled trials and non-randomized clinical trials
	Single-arm studies
	Full economic evaluations (e.g., cost-effectiveness, cost-utility, and cost–benefit analyses)
	Partial economic evaluations/cost analyses (e.g., cost-of-illness, cost-minimization, cost-consequence, and budget impact analyses)
	Pooled analyses presenting cost or resource use estimates
	Health technology assessment documents
	Literature reviews summarizing results of primary research studies and/or economic evaluations[a]
	Exclude:
	Studies with no relevant outcomes
	Publication types not of interest (i.e., comment, editorial, letter, case report, animal studies, pharmacokinetic-pharmacodynamics studies, dose estimation/dose-escalation studies without cost data)

[a]Literature reviews that involve some type of methodology for study identification and study selection were of interest. This included systematic literature reviews, structured literature reviews, scoping reviews, and landscape reviews. Narrative reviews that did not involve study identification via databases and primarily summarize an author's viewpoints were not of interest

characteristics of the included studies is given in Table 5 [10, 21–41].

Receipt of no intervention, best supportive care (BSC), or palliative care was of interest in this natural history review of patients with SMA types 1, 2, and 3. Although the ENDEAR clinical trial compared nusinersen with a sham procedure that consisted of a small needle prick on the lower back at the location at which the intrathecal injection of nusinersen is normally made, only data from the sham-controlled arm were extracted and reported for the natural history review [10, 21–25]. The remaining 16 natural history studies were non-interventional and did not report details of any background treatment or supportive care that patients received.

SMA Disease Type

Five studies reported patient characteristics for patients with SMA type 1 (Table 6) [10, 26–29]. Nine studies in the review reported patient characteristics for those with SMA types 2 and 3 (Table 7) [29, 31–40, 42]. Finkel et al. [27] evaluated both SMA types 1 and 2, reporting data separately for SMA type 1 and for subgroups of SMA type 1: type 1B (symptom onset at <3 months of age) and type 1C (symptom onset at >3 months of age). These categories were then further broken down by "recent" (enrolled within 3 months of diagnosis) or "chronic" (enrolled beyond 3 months of diagnosis) SMA. For SMA type 1, the average age of patients at the time of study enrollment ranged from 131 days to 59 months, whereas for SMA types 2 and 3, the average age of patients ranged from 4.6 to 35.57 years. Piepers et al. [41]

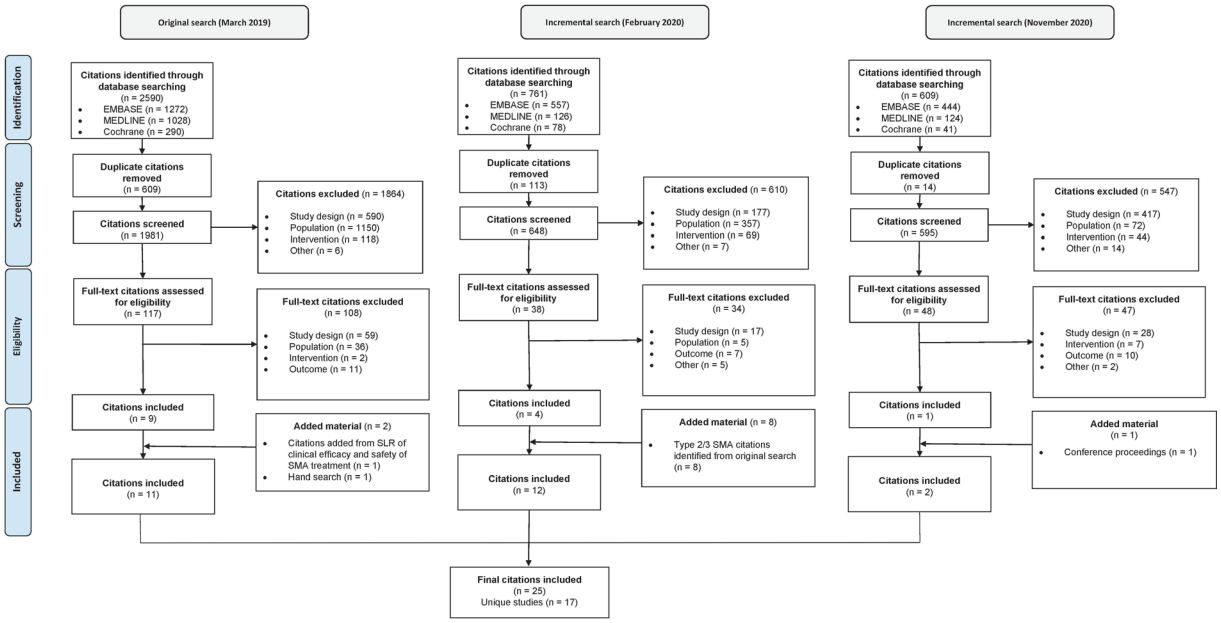

Fig. 1 Study selection flow diagram for natural history review

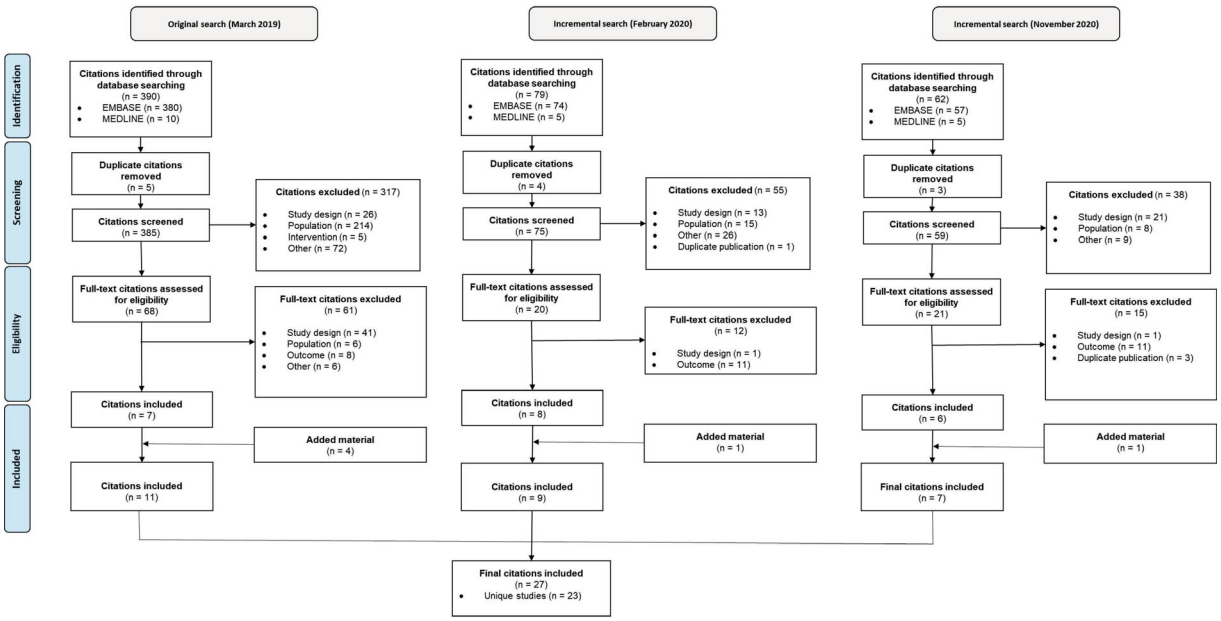

Fig. 2 Study selection flow diagram for health-related quality of life review

assessed SMA type 3B (symptom onset at >3 years of age) and type 4 (symptom onset at >19 years of age). For SMA type 3B, the age at onset ranged from 10–16 years, and the age at onset for SMA type 4 ranged from 27–34 years [41]. Finally, Wijngaarde et al. [43] assessed SMA types 1, 2, 3, and 4 and separately reported data by SMA subtypes 1A, 1B, 1C, 2A, 2B, 3A, and 3B. The classification of SMA type and subtype in this study was based on age at symptom onset

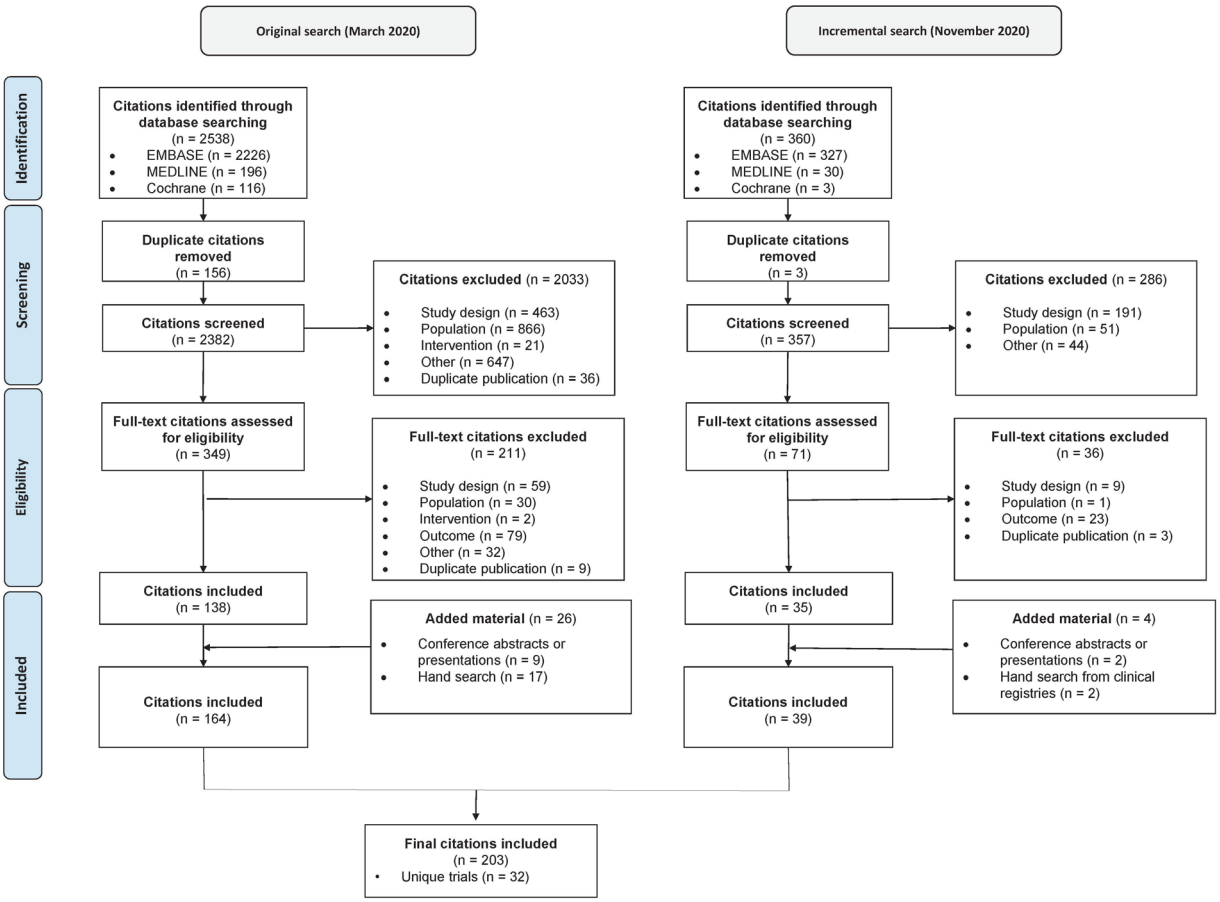

Fig. 3 Study selection flow diagram for clinical review

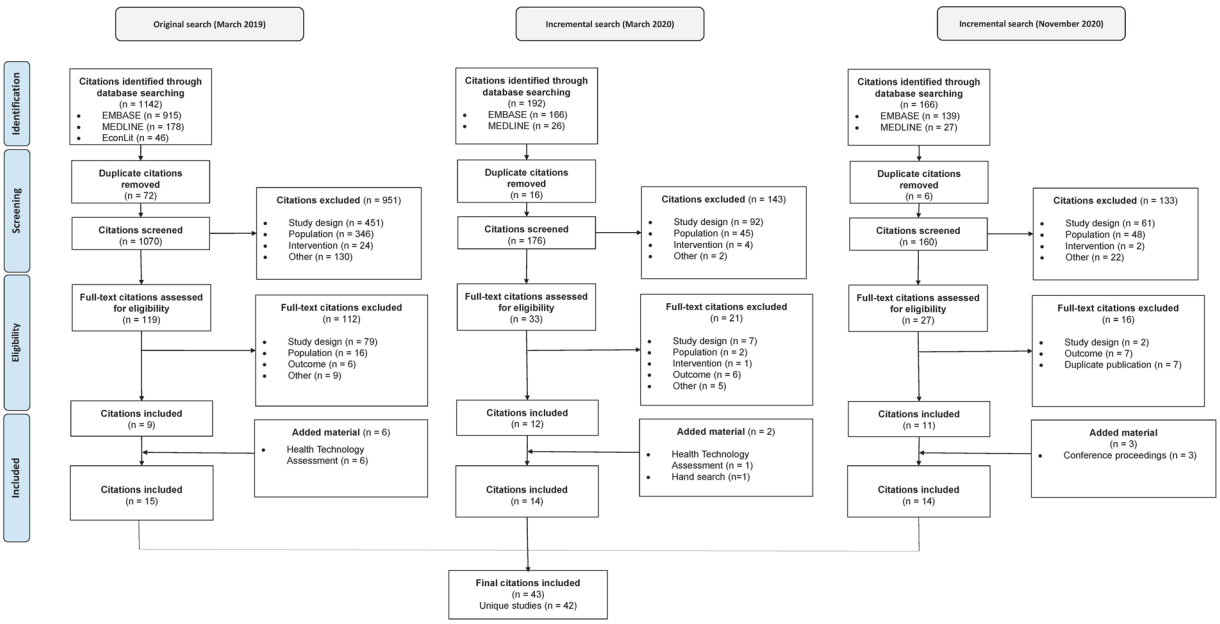

Fig. 4 Study selection flow diagram for economic review

Table 5 Study characteristics for the natural history review of SMA types 1, 2, and 3

Study name	Study design	SMA type(s)	Treatment(s) received
ENDEAR [10, 21–25]	Randomized controlled trial	Type 1	Sham control
Finkel [27]	Prospective cohort	Types 1 and 2	None
Finkel [28]	Prospective longitudinal	Type 1	None
NeuroNEXT [26]	Prospective cohort w/healthy control	Type 1	None
Alvarez [29]	Prospective cohort	Types 1, 2, and 3	None
Exposito [30]	Longitudinal cohort	Types 2 and 3	None
Pera [31]	Longitudinal cohort	Types 2 and 3	None
Piepers [41]	Prospective longitudinal	Types 3B and 4	None
Mercuri [32]	Prospective cohort	–	None
NatHis-SMA [33, 34]	Prospective cohort	Types 2 and 3	None
Kaufmann [35]	Prospective cohort	Types 2 and 3	None
Mazzone [36]	Prospective cohort	Types 2 and 3	None
Mazzone [37]	Prospective, longitudinal cohort	Type 3	None
ULENAP [38]	Longitudinal cohort	Types 2 and 3	None
Sivo [39]	Longitudinal cohort	Types 2 and 3	None
Montes [40]	Prospective, longitudinal cohort	Type 3	None
Kaufmann [42]	Prospective cohort	Types 2 and 3	None
Wijngaarde [43]	Longitudinal cohort	Types 1, 2, 3 and 4	None

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and highest acquired motor developmental milestones.

Outcome Reporting

Survival, including overall and event-free survival, was assessed in five studies, motor function in 15 studies, ventilation support in seven studies, and nutritional support in two studies (Table 8) [10, 26–41, 43]. Five studies (ENDEAR [10], Finkel et al. [27], Finkel et al. [28], NeuroNEXT [26], and Wijngaarde et al. [43]) reported some form of overall survival or event-free survival outcome, as summarized in Table 8. Overall survival was defined as the percentage of the population alive at the study's last follow-up endpoint. Event-free survival was defined as the percentage of patients who had not reached the combined endpoint of death or need for a minimum of 16 h/day of permanent ventilation support. Wijngaarde et al. [43] also assessed the combined endpoints of death or the need for a minimum of 12 h/day of permanent ventilation support and death or the need for nocturnal ventilation. Event-free survival was generally not reported in the analysis populations for natural history studies during the time points measured, except for two studies. Finkel et al. [27] reported 14 months of event-free survival for patients with SMA type 1C. Wijngaarde et al. [43] reported a median event-free survival of 9 days for patients with SMA type 1A, 7.7 months for patients with SMA type 1B, and 17 years for patients with SMA type 1C. Median event-free survival was not achieved for patients with SMA types 2, 3, and 4 in Wijngaarde et al. [43]. Overall survival for patients with SMA type 1 ranged from

Table 6 Patient characteristics for natural history review of SMA type 1

Study name	SMA type(s)	*N*	Median age at study onset[a]	Female, *n* (%)	White, *n* (%)
ENDEAR [10]	Type 1	41	181[b] days (6.0 months)	24 (59)	NR
Finkel [27]	Type 1B recent	6	6.5 months	1 (17)	NR
Finkel [27]	Type 1B chronic	10	30.5 months	2 (20)	NR
Finkel [27]	Type 1C recent	8	5 months	6 (75)	NR
Finkel [27]	Type 1C chronic	10	59 months	6 (60)	NR
Finkel [28]	Type 1	7	131 days (4.3 months)	NR	NR
NeuroNEXT [26]	Type 1	26	3.7[b] months	15 (58)	24 (92)
Alvarez [29]	Type 1B	15	NR	6 (40)	NR
Alvarez [29]	Type 1C	8	NR	4 (50)	NR
Wijngaarde [43]	Type 1A	3	NR	2 (67)	NR
Wijngaarde [43]	Type 1B	35	NR	20 (57)	NR
Wijngaarde [43]	Type 1C	32	NR	13 (41)	NR

NR not reported; *SMA* spinal muscular atrophy

[a]Mean age at study onset reported in days was converted to months by dividing the number of days by 30.25 and reported in parentheses

[b]Mean value

5.3–8 months, 6–12 months for patients with type 1B (177 months for chronic type 1B), and 11.5–32 months for patients with type 1C [10, 26–28, 43].

Motor function assessments (summarized in Table 9) were conducted in 15 of 17 studies [10, 26–41, 43]. The most commonly reported motor function measurements included Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), Hammersmith Functional Motor Scale (HFMS), HFMS expanded, the Revised Upper Limb Module, Motor Function Measure (MFM), Gross MFM, and the 6-min walk test.

Ventilation support was captured by seven studies [10, 24, 26–29, 33, 43], but they varied in definition. The ENDEAR trial [10, 21–25] captured the use of ventilator support at baseline and reported use of permanent assisted ventilation at the end of the study's follow-up. Finkel et al. [27] reported the percentage of patients who received ventilation support (non-invasive ventilation or intubation), Finkel et al. [28] reported the percentage of patients who required >16 h of mechanical ventilator support, and NeuroNEXT [26] reported the percentage of patients who needed intubation during the study's follow-up. Alvarez et al. [29] summarized ventilator support outcomes during the study, whereas NatHis-SMA [33, 34] reported these outcomes at baseline. Finally, Wijngaarde et al. [43] reported the percentage of patients who depended on at least ≥8–12 h of mechanical ventilation or nocturnal mechanical ventilation. This study also reported the ventilator dependency rate at various time points during the follow-up [43]. Only two studies captured information on nutritional support (Table 8).

Finkel et al. [27] and ENDEAR [10, 21–25] reported on the use of the gastrointestinal tube, with the latter revealing this outcome at baseline only. Quality assessments of the studies are covered in the Supplementary Material.

Table 7 Patient characteristics for natural history review of SMA types 2 and 3

Study name	SMA type(s)	*N*	Median age at study onset	Female, *n* (%)	White, *n* (%)
Alvarez [29]	Type 2	36	NR	24 (59)	NR
Alvarez [29]	Type 3A	23	NR	1 (17)	NR
Alvarez [29]	Type 3B	10	NR	2 (20)	NR
Pera [31]	Types 2 and 3	114	13.3 years	NR	NR
Pera [31]	Type 2 non-sitters	6	14.2 years	NR	NR
Pera [31]	Type 2 sitters	54	11.22 years	NR	NR
Pera [31]	Type 3 non-ambulant	22	18.1 years	NR	NR
Pera [31]	Type 3 ambulant	32	13.4 years	NR	NR
NatHis-SMA [33, 34]	Types 2 and 3	81	7.1 years	NR	NR
NatHis-SMA [33, 34]	Type 2 non-sitters	19	14.9 years	NR	NR
NatHis-SMA [33, 34]	Type 2 sitters	34	4.6 years	NR	NR
NatHis-SMA [33, 34]	Type 3 non-ambulant	9	19.6 years	NR	NR
NatHis-SMA [33, 34]	Type 3 ambulant	19	10.4 years	NR	NR
Kaufmann [35][a]	Type 2	41	9.1 years	NR (61)	NR (68)
Kaufmann [35][a]	Type 3	38	13.7 years	NR (45)	NR (82)
Kaufmann [35][a]	Types 2 and 3	79	11.3 years	NR (53)	NR (75)
Kaufmann [42][a]	Type 2	35	9.6 years	NR (60)	NR (69)
Kaufmann [42][a]	Type 3	30	13.2 years	NR (50)	NR (80)
Kaufmann [42][a]	Types 2 and 3	65	11.2 years	NR (55)	NR (74)
Mazzone [36]	Types 2 and 3	74	8.62 years	NR	NR
Mazzone [37]	Type 3	38	14.07 years	NR	NR
Mazzone [37]	Type 3A	31	9.21 years	NR	NR
Mazzone [37]	Type 3B	7	35.57 years	NR	NR
ULENAP [38]	Type 2	16	15.4 years	NR (63)	NR
ULENAP [38]	Type 3	7	19.9 years	NR (71)	NR
Sivo [39]	Types 2 and 3	74	10.22 years	NR	NR
Montes [40]	Type 3	73	13.5 years	NR (45)	NR
Montes [40]	Type 3A	52	7.9 years	NR (58)	NR
Montes [40]	Type 3B	21	27.3 years	NR (14)	NR
Mercuri [32]	–	506	NR	NR	NR
Wijngaarde [43]	Type 2A	75	NR	45 (60)	NR
Wijngaarde [43]	Type 2B	51	NR	33 (65)	NR
Wijngaarde [43]	Type 3A	62	NR	33 (53)	NR

Table 7 continued

Study name	SMA type(s)	*N*	Median age at study onset	Female, *n* (%)	White, *n* (%)
Wijngaarde [43]	Type 3B	40	NR	18 (45)	NR

NR not reported, *SMA* spinal muscular atrophy
[a]Kaufmann 2011 [42] and Kaufmann 2012 [35] report results from the same study, but with different follow-ups

Table 8 Outcome reporting for natural history review

Study name	Treatment	Overall survival	Event-free survival	Achievement or deterioration of motor milestones	Ventilation support	Nutritional support
ENDEAR [10]	Sham-controlled	✔	✔	✔	✔	✔
Finkel [27]	None	✔	✔	✔	✔	✔
Finkel [28]	None	✔	✔		✔	
NeuroNEXT [26]	None	✔	✔	✔	✔	
Alvarez [29]	None			✔	✔	
Exposito [30]	None			✔		
Pera [31]	None			✔		
Piepers [41]	None					
Mercuri [32]	None			✔		
NatHis-SMA [33, 34]	None			✔	✔	
Kaufmann [35]	None			✔		
Mazzone [36]	None			✔		
Mazzone [37]	None			✔		
ULENAP [38]	None			✔		
Sivo [39]	None			✔		
Montes [40]	None			✔		
Wijngaarde [43]	None	✔	✔		✔	

Table 9 Outcome reporting for natural history review: motor milestones

Study name	SMA type(s)	*N*	Achievement or deterioration of motor milestones, *n* (%)	Motor function change over time
ENDEAR [10]	Type 1	37	✔	✔
Finkel [27]	Type 1	34	✔[a]	✔
Finkel [28]	Type 1	7		
NeuroNEXT [26]	Type 1	26	✔[a]	✔[a]
Alvarez [29]	Type 2	36	✔	
Alvarez [29]	Type 3	33	✔	
Exposito [30]	Type 2	32	✔	
Pera [31]	Type 2	60	✔	
Piepers [41]	Types 3B and 4	12		✔
Mercuri [32]	–	506	✔	
NatHis-SMA [33, 34]	Type 2	24	✔	
Kaufmann [35]	Type 3	8	✔	
Mazzone [36]	Types 2 and 3	73	✔	
Mazzone [37]	Type 3	38	✔	
ULENAP [38]	Type 2	16	✔	
ULENAP [38]	Type 3	7	✔	
Sivo [39]	Types 2 and 3	74	✔	
Montes [40]	Type 3	73	✔	

SMA spinal muscular atrophy
[a]Outcomes presented as graphical data listed as figure location in corresponding publication

Systematic Literature Review of HRQOL and Utilities

Study Selection and Overview

Figure 2 presents the PRISMA flow diagram of the study selection process for the original and updated search to identify studies that described the humanistic burden of SMA. A total of 23 unique studies were included in the review, which corresponded to 27 publications (Fig. 2; Table 10) [44–70]. These publications included two SLRs (Landfeldt et al. [56], Wadman et al. [67]). Wadman et al. [67] reviewed trials that evaluated the safety and efficacy of drug treatments for SMA types 2 and 3 and reported a change in HRQOL as a secondary outcome, whereas Landfeldt et al. [56] conducted a systematic review of studies reporting HRQOL outcomes for all SMA types. Of the remaining unique 21 studies, 12 used the Pediatric Quality of Life Inventory (PedsQL) as an HRQOL measure. Other study characteristics of the included studies are described in Table 11 [44–69]. Eight studies assessed the impact of DMTs on the HRQOL of patients with SMA, and these are summarized below. Overall, there was limited evidence available on the impact of DMTs on HRQOL.

Outcome Reporting

In an abstract presented at the American Academy of Neurology in 2020, Belter et al. [44]

Table 10 Studies included in the review of health-related quality of life and utilities, with associated publications

Study name	Primary publication	Title	Secondary publication
Belter [44]	Belter et al. [44]	Health utility index scores in treated and untreated patients with spinal muscular atrophy: findings from the 2019 Cure SMA community update survey	–
Bermudez [45]	Bermudez et al. [45]	Quality of life in adults with spinal muscular atrophy	–
Bertini [46]	Bertini et al. [46]	Safety and efficacy of olesoxime in patients with type 2 or non-ambulatory type 3 spinal muscular atrophy: a randomised, double-blind, placebo-controlled phase 2 trial	–
Binz [47]	Binz et al. [47]	An observational cohort study on impact, dimensions and outcome of perceived fatigue in adult 5q-spinal muscular atrophy patients receiving nusinersen treatment	–
SMA CARNI-VAL Part 1 [48]	Swoboda et al. [48]	SMA CARNI-VAL trial part I: double-blind, randomized, placebo-controlled trial of L-carnitine and valproic acid in spinal muscular atrophy	–
SMA CARNI-VAL Part 2 [49]	Kissel et al. [49]	SMA CARNI-VAL trial part II: a prospective, single-armed trial of L-carnitine and valproic acid in ambulatory children with spinal muscular atrophy	–
CHERISH [50, 51]	Johnson et al. [50]	Impact of caregiver experience and HRQOL in later-onset spinal muscular atrophy (SMA): results from the phase 3 CHERISH trial	Johnson et al. [51]
Chiriboga [52]	Chiriboga et al. [52]	Results from a phase 1 study of nusinersen (ISIS-SMN(Rx)) in children with spinal muscular atrophy	–
CS2/CS12 [53]	Kirschner et al. [53]	Nusinersen experience in individuals with spinal muscular atrophy type III: a case series	–
Hernandez-Rojo Claverie [54]	Hernandez-Rojo Claverie et al. [54]	Impact of the disease on quality of life in patients with spinal muscular atrophy	–
Klug [55]	Klug et al. [55]	Disease burden of spinal muscular atrophy in Germany	–
Landfeldt [56]	Landfeldt et al. [56]	Quality of life of patients with spinal muscular atrophy: a systematic review	–
Lloyd [57, 58]	Lloyd et al. [57]	Estimation of the quality of life benefits associated with treatment for spinal muscular atrophy	Lloyd et al. [58]
López-Bastida [59]	López-Bastida et al. [59]	Social/economic costs and health-related quality of life in patients with spinal muscular atrophy (SMA) in Spain	–
Love [60]	Love et al. [60]	Utility based health related quality of life in children and adolescents with spinal muscular atrophy	–

Table 10 continued

Study name	Primary publication	Title	Secondary publication
Malone [61, 62]	Malone et al. [61]	ND2 Cost-utility analysis of single dose gene-replacement therapy for spinal muscular atrophy type 1 compared to chronic nusinersen treatment	Malone et al. [62]
SHINE [63]	Montes et al. [63]	Impact of continued nusinersin treatment on caregiver experience and health-related quality of life in later-onset SMA: results from the SHINE study	–
Strauss [64]	Strauss et al. [64]	Preliminary safety and tolerability of a novel subcutaneous intrathecal catheter system for repeated outpatient dosing of nusinersen to children and adults with spinal muscular atrophy	–
Thokala [65]	Thokala et al. [65]	Cost-effectiveness of nusinersen for patients with infantile-onset spinal muscular atrophy in US	–
Thompson [66]	Thompson et al. [66]	The utility of different approaches to developing health utilities data in childhood rare diseases — a case study in spinal muscular atrophy (SMA)	–
Wadman [67]	Wadman et al. [67]	Drug treatment for spinal muscular atrophy types ii and iii	–
Weaver [68]	Weaver et al. [68]	A prospective, crossover survey study of child- and proxy-reported quality of life according to spinal muscular atrophy type and medical interventions	–
Zuluaga-Sanchez [69] and Zuluaga [70]	Zuluaga-Sanchez et al. [69]	Cost-effectiveness of nusinersen in the treatment of patients with infantile-onset and later-onset spinal muscular atrophy in Sweden	Zuluaga et al. [70]

HRQOL health-related quality of life, *L-carnitine* levocarnitine, *SMA* spinal muscular atrophy

reported HRQOL among patients with SMA types 1 to 3 based on 281 responses collected in the Cure SMA community update survey in 2019. The HRQOL measures included Health Utilities Index Mark 2 (HUI2) and HUI3, which were described for patients with treatment versus patients without treatment by SMA type. Patients with treatment had greater HRQOL scores across all SMA types compared with patients not receiving treatment, although treatment information was not disclosed in the abstract.

Bertini et al. [46] examined HRQOL among patients with SMA types 2 and 3 as part of a multicenter Phase II RCT that studied the effects of olesoxime versus placebo. Participants had to have been between 3 and 25 years of age, had type 2 or non-ambulatory type 3 SMA, and had an MFM relative score of ≥15% and an HFMS score between 3 and 38, with onset of SMA symptoms at 3 years of age or younger. HRQOL was measured using the PedsQL Neuromuscular Module, including both patient- and parent-reported assessments. Of 158 included patients, 136 completed at least a baseline rating and one follow-up HRQOL rating. The difference in change in HRQOL from baseline between the olesoxime and placebo groups was not statistically significant for any subpopulation by age or subscore by PedsQL module. However, because scores were reported as differences in change

Table 11 Study characteristics for the health-related quality of life review of SMA types 1, 2, and 3

Study name	Study type	SMA type(s)	Agent type	HRQOL measures
Belter [44]	Cross-sectional	Types 1, 2, and 3	–	HUI
Bermudez [45]	Clinical trial	Ambulatory and non-ambulatory	–	SF-36
Bertini [46]	RCT	Types 2 and 3	Olesoxime Placebo	PedsQL
Binz [47]	Prospective cohort	Types 2, 3, and 4	Nusinersen	EQ-5D
SMA CARNI-VAL Part 1 [48]	RCT	Type 2 or non-ambulatory type 3	VPA + L-carnitine Placebo	PedsQL
SMA CARNI-VAL Part 2 [49]	Open-label	Type 3	VPA + L-carnitine	PedsQL
CHERISH [50, 51]	RCT	Types 2 and 3	Nusinersen Sham control	ACEND, PedsQL
Chiriboga [52]	Open-label	Types 2 and 3	Nusinersen	PedsQL
Hernandez-Rojo Claverie [54]	Interview	Types 3 and 4	Nusinersen	EQ-5D, SF-36
Kirschner [53]	Case series	Type 3	Nusinersen	PedsQL
Klug [55]	Cross-sectional	Types 1, 2, and 3	–	PedsQL
Landfeldt [56]	Systematic review	Types 1, 2, and 3	–	–
Lloyd [57, 58]	Clinician survey	Types 1 and 2	–	Health utilities
López-Bastida [59]	Cross-sectional	Types 1, 2, and 3	–	EQ-5D for patients and caregivers
Love [60]	Patient/caregiver survey	All types	–	HUI
Malone [61, 62]	Cost-effectiveness analysis	Type 1	Onasemnogene abeparvovec Nusinersen	PedsQL, EQ-5D-Y, EQ-5D
SHINE [63]	Open-label	Later-onset SMA	Nusinersen	ACEND, PedsQL
Strauss [64]	Prospective cohort	Types 2 and 3	Nusinersen	PedsQL
Thokala [65]	Cost-effectiveness analysis	Infantile-onset	Nusinersen BSC	Health utilities
Thompson [66]	Mixed methods	Types 1, 2, and 3	–	Health utilities
Wadman [67]	Systematic review	Types 2 and 3	–	–

Table 11 continued

Study name	Study type	SMA type(s)	Agent type	HRQOL measures
Weaver [68]	Randomized survey	Types 1, 2, and 3	PedsQL 3.0 Neuromuscular Module CPCHILD survey	PedsQL
Zuluaga-Sanchez [69]	Vignette study	Infantile-onset, later-onset	Nusinersen Standard of care	PedsQL, NIH toolbox: emotion domain

ACEND Assessment of Caregiver Experience with Neuromuscular Disease, *BSC* best supportive care, *CPCHILD* Caregiver Priorities and Child Health Index of Life with Disabilities, *EQ-5D* EuroQoL 5 Dimension, *EQ-5D-Y* EuroQoL 5 Dimension Youth Version, *HRQOL* health-related quality of life, *HUI* health utilities index, *L-carnitine* levocarnitine, *NIH* National Institutes of Health, *PedsQL* Pediatric Quality of Life Inventory, *RCT* randomized controlled trial, *SF-36* Short-Form 36, *SMA* spinal muscular atrophy, *VPA* valproic acid

from baseline between treatment groups, there is no indication whether HRQOL improved or declined in either group, respectively. Study authors concluded that no clear benefit of olesoxime treatment was observed regarding HRQOL outcomes. However, the authors also asserted that the validity and sensitivity of the PedsQL had not been fully established in patients with SMA.

Johnson et al. [50, 51] examined the impact on caregivers through Assessment of Caregiver Experience with Neuromuscular Disease (ACEND) scores and changes in HRQOL through the parent version of PedsQL using data from the CHERISH trial, which randomized children aged 2 to 12 years of age with SMA types 2 and 3 to nusinersen or control (sham procedure). The change in ACEND (least squares mean difference) was measured in seven subdomains at 6 and 15 months. HRQOL was measured using the PedsQL Generic Core Scale and Neuromuscular Module through parent-reported assessments. A reduced impact on caregivers in the nusinersen arm was reported over time in three ACEND subdomains: feeding/grooming/dressing, transfer, and mobility. The decline in PedsQL scores for the nusinersen arm was reported to be less than the decline in scores in the sham control arm from baseline to month 15.

Montes et al. [63] examined change in HRQOL for patients with later-onset SMA and the impact on caregivers based on data from SHINE and CHERISH. SHINE is an open-label extension study that enrolled patients from multiple completed clinical trials, including CHERISH, EMBRACE, and ENDEAR. HRQOL was measured using the caregiver-reported PedsQL Generic Core Scale and Neuromuscular Module for patients from the nusinersen-treated group in CHERISH. Impact on caregivers was measured using ACEND scores among parents of the same patient population. Both PedsQL and ACEND scores were compared between baseline and day 1170 of CHERISH. For ACEND, only five out of seven subdomain scores were reported. This study also stated that greater benefits in caregiver impact were observed among patients who initiated nusinersen earlier (aged $\geq$2 and <3.5 years) than later (aged $\geq$3.5 and <5 years) in six out of seven ACEND subdomains. However, the corresponding ACEND scores were not reported. Quality assessments of the studies are contained in the Supplementary Material.

Swoboda et al. [48] examined HRQOL among patients with SMA types 2 and 3 in Part 1 of SMA CARNI-VAL, a multicenter Phase II RCT that examined the effects of valproic acid (VPA) and levocarnitine (L-carnitine) versus placebo in non-ambulatory pediatric patients with SMA types 2 or 3 who were aged 2 to 8 years and had Modified HFMS (MHFMS) scores between 2 and 37. HRQOL was measured using the PedsQL,

Table 12 Study characteristics for the clinical review

Study name	NCT code	Study design	Intervention	SMA type(s)
Bertini [46]	NCT01302600	RCT	Olesoxime	Type 2 and non-ambulatory type 3
Chen [71]	NCT00485511	RCT	Hydroxyurea	Types 2 and 3
CHERISH [50]	NCT02292537	RCT	Nusinersen	Types 2 and 3
Chiriboga [72]	NCT01645787	RCT, crossover	4-Aminopyridine	Types 1, 2, and 3
CS1 [52]	NCT01494701	Non-randomized, dosage-escalation	Nusinersen	Later-onset (have or most likely to develop types 2 or 3)
CS2/CS12 [73]	NCT01703988	Single-arm	Nusinersen	Types 2 and 3
CS3A [74]	NCT01839656	Open-label, dosage-escalation	Nusinersen 6–12 mg	Type 1
CS10 [52]	NCT01780246	Single-arm	Nusinersen	Types 2 and 3
CY 5021 [75]	NCT02644668	RCT	Reldesemtiv	Types 2, 3, and 4
EMBRACE [76]	NCT02462759	RCT	Nusinersen	Types 1 and 2; two or three *SMN2* gene copies
ENDEAR [10]	NCT02193074	RCT	Nusinersen	Type 1; two copies of *SMN2* gene
FIREFISH Part 1 [77]	NCT02913482	Single-arm	Risdiplam	Type 1; two copies of *SMN2* gene
Frongia [78]	NR	NR	Salbutamol	Type 2
JEWELFISH [79]	NCT03032172	Open-label	Risdiplam	Types 2 and 3
Kirschner [80]	NCT00533221	RCT, crossover	Somatropin	Types 2 and 3
Krosschell [81]	NCT00661453	Open-label	VPA + L-carnitine	Type 1
LMI070X2201 [82]	NCT02268552	Open-label	Branaplam	Type 1
LT-001 [83]	NCT03421977	Observational	Onasemnogene abeparvovec	Type 1; two copies of *SMN2* gene
NURTURE [84, 85]	NCT02386553	Open-label	Nusinersen	Presymptomatic (15/25 with two copies of *SMN2* gene; 10/25 with three copies of *SMN2* gene)
OLEOS [86]	NCT02628742	Open-label	Olesoxime	Type 2 and non-ambulatory type 3
Russman [87]	NR	RCT	Riluzole	Type 1

Table 12 continued

Study name	NCT code	Study design	Intervention	SMA type(s)
SHINE [63, 88]	NCT02594124	Open-label	Nusinersen	Infantile- and later-onset (types 1, 2, and 3)
SMA CARNI-VAL Part 1 [48]	NCT00227266	RCT	VPA + L-carnitine	Type 2 and type 3 non-ambulatory
SMA CARNI-VAL Part 2 [49]	NCT00227266	Open-label	VPA + L-carnitine	Types 2 and 3
SPR1NT [89]	NCT03505099	Open-label, single-arm	Onasemnogene abeparvovec	Presymptomatic with two or three copies of *SMN2* gene
START (CL-101) [12, 90, 91]	NCT02122952	Open-label, dose-escalation	Onasemnogene abeparvovec	Type 1; two copies of *SMN2* gene
STR1VE-EU [92]	NCT03461289	Open-label, single-arm	Onasemnogene abeparvovec	Type 1, one or two copies of *SMN2* gene
STR1VE-US [93]	NCT03306277	Open-label, single-arm	Onasemnogene abeparvovec	Type 1; one or two copies of *SMN2* gene
STRONG [94]	NCT03381729	Single-arm	Onasemnogene abeparvovec	Type 2 and type 3; three copies of *SMN2* gene
SUNFISH Part 1 [95]	NCT02908685	RCT	Risdiplam	Types 2 and 3
Swoboda [96]	NCT00374075	Open-label	VPA	Types 1, 2, and 3
Tiziano [97]	N/A	RCT	Salbutamol	Type 3

L-carnitine levocarnitine, *NCT* national clinical trial, *N/A* not applicable, *NR* not reported, *RCT* randomized controlled trial, *SMA* spinal muscular atrophy, SMN2 *survival motor neuron 2* gene, *VPA* valproic acid

including both patient-reported and parent-reported assessments at baseline, but just parent-reported assessments at 6 months of follow-up. The number of patients completing HRQOL assessments varied across PedsQL subscales. Overall, the change from baseline in parent-reported PedsQL scores was not significantly different between treatment groups (VPA + L-carnitine and placebo). No clear benefit of VPA + L-carnitine was observed with regard to HRQOL. Although PedsQL total HRQOL ratings did not improve as MHFMS improved, there was evidence of deterioration of HRQOL as MHFMS declined over time.

Kissel et al. [49] examined HRQOL in Part 2 of SMA CARNI-VAL, an open-label trial conducted in parallel with Part 1, in which all patients received a VPA and L-carnitine combination regimen. Eligible participants had SMA type 2 or 3, were 3 to 17 years of age, and were capable of standing independently for at least 2 s. HRQOL was assessed using the PedsQL, including both patient- and parent-reported assessments. Data were provided only for patient-reported PedsQL ratings, but the authors noted that there was no

Table 13 Patient characteristics for clinical review

Study name	SMA type(s)	Treatment	*N*	Mean age at study onset[a]	Female, *n* (%)	White, *n* (%)
Bertini [46]	Types 2 and non-ambulatory type 3	Olesoxime	103	9.1 years	48 (47)	NR
		Placebo	57	11.2 years	32 (56)	NR
Chen [71]	Types 2 and 3	Hydroxyurea	37	16.6 years	20 (54)	NR
		Placebo	20	14.6 years	11 (55)	NR
CHERISH [50]	Types 2 and 3	Nusinersen	84	4 years[b]	46 (55)	64 (76)
		Sham procedure	42	3 years[b]	21 (50)	30 (71)
Chiriboga [72]	Types 1, 2, and 3	Overall (4-aminopyridine and placebo)	11	37.7 years	5 (45)	NR
CS1 [52]	Types 2 and 3	Nusinersen 1 mg	6	7.7 years	1 (17)	5 (83)
		Nusinersen 3 mg	6	5.3 years	5 (83)	6 (100)
		Nusinersen 6 mg	6	6 years	5 (83)	5 (83)
		Nusinersen 9 mg	10	5.8 years	6 (60)	7 (70)
CS10 [52]	Later-onset SMA (types 2 and 3)	Nusinersen	24	NR	NR	NR
CS2/CS12 [73]	Types 2 and 3	Nusinersen	28	7.1 months	13 (46)	NR
CS3A [74]	Type 1	Nusinersen 6–12 mg	4	145 days (4.8 months)	1 (25)	3 (75)
		Nusinersen 12 mg	16	140 days (4.6 months)	7 (44)	13 (81)
CY 5021 [75]	Types 2, 3, and 4	Reldesemtiv 150 mg	24	27.8 years	10 (42)	23 (96)
		Reldesemtiv 450 mg	20	32.6 years	8 (40)	18 (90)
		Placebo	26	28.5 years	11 (42)	22 (85)
EMBRACE [76]	Types 1 and 2; two or three *SMN2* gene copies	Nusinersen	14	NR	NR	NR
		Placebo	7	NR	NR	NR
ENDEAR [10]	Type 1; two copies of *SMN2* gene	Nusinersen	81	163 days (5.4 months)	43 (54)	NR
		Sham procedure	41	181 days (6.0 months)	24 (59)	NR
FIREFISH Part 1 [77]	Type 1; two copies of *SMN2* gene	Risdiplam	21	6.7 months[b]	15 (71)	NR
Frongia [78]	Type 2	Salbutamol	48	10 years	NR	NR
JEWELFISH [79]	Types 2 and 3	Risdiplam	10	NR	NR	NR

Table 13 continued

Study name	SMA type(s)	Treatment	*N*	Mean age at study onset[a]	Female, *n* (%)	White, *n* (%)
Kirschner [80]	Types 2 and 3	Overall (somatropin and placebo arms)	10	14.7 years	7 (36.8)	NR
Krosschell [81]	Type 1	VPA + L-carnitine	37	5.8 years[b]	17 (46)	33 (89)
LMI070X2201 [82]	Type 1	Branaplam	14	NR	NR	NR
LT-001 [83]	Type 1; two copies of *SMN2* gene	Onasemnogene abeparvovec	13	2.5 years	7 (53.8)	12 (92.3)
NURTURE [84, 85]	Presymptomatic (15/25 with two *SMN2* copies; 10/25 with three *SMN2* copies)	Nusinersen	25	22 days[b] (0.7 month)	13 (52)	NR
OLEOS [86]	Type 2 and non-ambulatory type 3	Olesoxime	128	14.5 years	65 (50.8)	NR
Russman [87]	Type 1	Riluzole	7	9.3 months	NR	NR
		Placebo	3	4.3 months	NR	NR
SHINE [63, 88]	Infantile-onset (type 1)	Nusinersen	89	NR	NR	NR
SMA CARNIVAL Part 1 [48]	Type 2 and type 3 non-ambulatory	VPA + L-carnitine	30	4.3 years	17 (56.7)	25 (83.3)
		Placebo	31	4.4 years	11 (35.5)	26 (83.9)
SMA CARNIVAL Part 2 [49]	Type 2 or 3	VPA + L-carnitine	33	6.9 years[b]	11 (33.3)	29 (87.9)
SPR1NT [89]	Presymptomatic two *SMN2* copies	Onasemnogene abeparvovec	14	20.6 days (0.7 month)	10 (71.4)	7 (50)
	Presymptomatic three *SMN2* copies		15	28.7 days (0.9 month)	9 (60)	10 (66.7)
	Presymptomatic four *SMN2* copies		1	36 days (1.2 months)	0	1 (100)
START (CL-101) [90, 91]	Type 1; two copies of *SMN2* gene	Onasemnogene abeparvovec 6.7×10^{13} vg/kg (low-dose)	3	6.3 months	2 (66.7)	3 (100)
		Onasemnogene abeparvovec 2.0×10^{14} vg/kg (high-dose)	12	3.4 months	7 (58)	11 (92)

Table 13 continued

Study name	SMA type(s)	Treatment	*N*	Mean age at study onset[a]	Female, *n* (%)	White, *n* (%)
STR1VE-EU [92]	Type 1, two copies of *SMN2* gene	Onasemnogene abeparvovec	33	4.06 months	19 (57.6)	NR
STR1VE-US [93]	Type 1; two copies of *SMN2* gene	Onasemnogene abeparvovec	22	3.7 months	12 (54.6)	11 (50)
STRONG [94]	Type 2 and type 3; three copies of *SMN2* gene	Onasemnogene abeparvovec (6.0×10^{13} vg)	3	17.2 months	2 (66.7)	2 (66.7)
		Onasemnogene abeparvovec (1.2×10^{14} vg): younger than 24 months	13	16.73 months	6 (46.2)	10 (76.9)
		Onasemnogene abeparvovec (1.2×10^{14} vg), between 24 and 60 months	12	37.51 months	6 (50)	8 (66.7)
		Onasemnogene abeparvovec (2.4×10^{14} vg)	4	16.85 months	0	3 (75)
SUNFISH Part 1 [95]	Types 2 and 3	Risdiplam	51	NR	27 (52.9)	NR
Swoboda [96]	Types 1, 2, and 3	VPA	42	5.7 years	NR	NR
Tiziano [97]	Type 3	Salbutamol	23	14.3 years	6 (26)	NR
		Placebo	22	10.7 years	11 (50)	NR

L-carnitine levocarnitine, *NR* not reported, *SMA* spinal muscular atrophy, SMN2 *survival motor neuron 2* gene, *VPA* valproic acid

[a]Mean age at study onset reported in days was converted to months by dividing the number of days by 30.25 and reported in parentheses

[b]Median age

Table 14 List of publications included in economic review

Study name	Year	Title	Country	Study type
Cost analyses				
Ali et al. [99]	2019	Healthcare utilisation in children with SMA type 1 treated with nusinersen: a single centre retrospective review	UK	Cost analysis
Armstrong et al. [100]	2016	The economic burden of spinal muscular atrophy	US	Cost analysis
Cardenas et al. [101]	2019	High healthcare resource use in hospitalized patients with a diagnosis of spinal muscular atrophy type 1 (SMA1): retrospective analysis of the Kids' Inpatient Database (KID)	US	Cost analysis
Chambers et al. [102]	2020	Prenusinersen economic and health-related quality of life burden of spinal muscular atrophy	Australia	Cost analysis
Chen et al. [103]	2020	A population-based study examining the epidemiologic burden, health care resource utilization and costs of spinal muscular atrophy in Alberta, Canada	Canada	Cost analysis
Dabbous et al. [104]	2018	Economic burden of infant-onset (type 1) spinal muscular atrophy: a retrospective claims database analysis	US	Cost analysis
Darbà [134]	2019	Patient characteristics and hospitalisation costs of spinal muscular atrophy in Spain: a retrospective multicentre database analysis	Spain	Cost analysis
Darbà [105]	2020	Direct medical costs of spinal muscular atrophy in the Catalonia region: a population-based analysis	Spain	Cost analysis
Droege et al. [106]	2020	Economic burden of spinal muscular atrophy in the United States: a contemporary assessment	US	Cost analysis
Droege et al. [107]	2020	Burden of illness of spinal muscular atrophy: an update	US	Cost analysis

Table 14 continued

Study name	Year	Title	Country	Study type
Goble et al. [108]	2018	The economic burden of spinal muscular atrophy patients in a commercially insured population in the United States	US	Cost analysis
Hall et al. [109]	2017	Healthcare resource utilization and costs of spinal muscular atrophy care in the US Medicaid population	US	Cost analysis
Klug et al. [55]	2016	Disease burden of spinal muscular atrophy in Germany	Germany	Cost analysis
Koch et al. [110]	1986	Outpatient rehabilitation for chronic neuromuscular diseases	US	Cost analysis
Kockaya et al. [111]	2019	Annual cost of treatment of spinal muscular atrophy patients in Turkey	Turkey	Cost analysis
Lee et al. [112]	2019	Pre-nusinersen hospitalization costs of children with spinal muscular atrophy	US	Cost analysis
López-Bastida et al. [59]	2017	Social/economic costs and health-related quality of life in patients with spinal muscular atrophy (SMA) in Spain	Spain	Cost analysis
McMillan et al. [113]	2020	Disease and treatment burden of spinal muscular atrophy (SMA) on patients and caregivers in Canada	Canada	Cost analysis
López-Bastida et al. [114] Peña-Longobardo et al. [115]	2019 [114], 2020 [115]	The economic impact and health-related quality of life of spinal muscular atrophy (SMA). An analysis across Europe	UK, France, and Germany	Cost analysis
Starner and Gleason [116]	2019	Spinal muscular atrophy: an integrated medical and pharmacy claims analysis of nusinersen uptake and gene therapy forecast among 15 million commercially insured	US	Cost analysis

Table 14 continued

Study name	Year	Title	Country	Study type
Economic evaluations				
Arjunji et al. [117]	2020	Cost-effectiveness analysis of newborn screening for spinal muscular atrophy in the United States	US	Cost-effectiveness analysis
Chen et al. [118]	2020	Cost-effectiveness analysis of newborn screening and treatment for spinal muscular atrophy	US	Cost-effectiveness analysis
Connock et al. [119]	2020	Will the US $5 million onasemnogene abeparvosec treatment for spinal muscular atrophy represent 'value for money' for the NHS? A rapid inquiry into suggestions that it may be cost-effective	UK	Cost-effectiveness analysis
Dabbous et al. [120]	2019	Cost-effectiveness and budget impact of onasemnogene abeparvovec for spinal muscular atrophy type 1: post-hoc analysis of a model developed by ICER	US	Cost-effectiveness analysis
Dean et al. [121]	2020	Cost-utility analysis of single dose gene-replacement therapy for spinal muscular atrophy type 1 compared to chronic nusinersen treatment in Japan	Japan	Cost-effectiveness analysis
Jalali et al. [122]	2020	Cost-effectiveness of nusinersen and universal newborn screening for spinal muscular atrophy	US	Cost-effectiveness analysis
Malone et al. [61]	2019	ND2 Cost-utility analysis of single dose gene-replacement therapy for spinal muscular atrophy type 1 compared to chronic nusinersen treatment	US	Cost-effectiveness analysis
Malone et al. [62]	2019	Cost-effectiveness analysis of using onasemnogene abeparvocec (AVXS-101) in spinal muscular atrophy type 1 patients	US	Cost-effectiveness analysis

Table 14 continued

Study name	Year	Title	Country	Study type
Thokala et al. [123]	2019	Cost-effectiveness of nusinersen and onasemnogene abeparvovec for infantile-onset spinal muscular atrophy (type I SMA) in the US	US	Cost-effectiveness analysis
Thokala et al. [65]	2020	Cost effectiveness of nusinersen for patients with infantile-onset spinal muscular atrophy in US	US	Cost-effectiveness analysis
Zuluaga-Sanchez et al. [69]	2019	Cost effectiveness of nusinersen in the treatment of patients with infantile-onset and later-onset spinal muscular atrophy in Sweden	Sweden	Cost-effectiveness analysis
Zuluaga Sanchez et al. [124]	2019	Improved quality of life and life-years in patients with infantile-onset SMA following treatment with nusinersen	US	Cost-effectiveness analysis
Zuluaga Sanchez et al. [125]	2019	Improved quality of life for patients and caregivers among patients with later-onset SMA following treatment with nusinersen	US	Cost-effectiveness analysis
NICE [19]	2018	Nusinersen for treating spinal muscular atrophy [ID1069]	UK (England and Wales)	Health technology assessment
SMC [126]	2018	Nusinersen 12 mg solution for injection (Spinraza®) [SMC No. 1318/18]	UK (Scotland)	HTA Agency Recommendation
CADTH [127]	2017	CADTH Canadian Drug Expert Committee Recommendation — Nusinersen (Spinraza — Biogen Canada Inc.)	Canada	Health technology assessment
Agency for the Quality and Accreditation in Health Care and Social Welfare [Agencija za kvalitetu I akreditaciju u zdravstvu I socijalnoy skrbi][a] [128]	2017	Nusinersen (Spinraza) in the treatment of patients with spinal muscular atrophy (SMA) [Nusinersen (Spinraza) u liječenju bolesnika sa spinalnom mišićnom atrofijom (SMA)]	Croatia	HTA Agency Recommendation

Table 14 continued

Study name	Year	Title	Country	Study type
Swedish Dental and Pharmaceutical Benefits Agency [Tandvårds- och läkemedelsförmånsverket, TLV][a] [129]	2017	Spinraza (nusinersen)	Sweden	HTA Agency Recommendation
National Centre for Pharmacoeconomics, Ireland [130]	2017	Cost-effectiveness of nusinersen (Spinraza) for the treatment of 5q spinal muscular atrophy (SMA)	UK (Ireland)	HTA Agency Recommendation
ICER [131]	2020	Spinraza® and Zolgensma® for spinal muscular atrophy: effectiveness and value	US	HTA Agency Recommendation
Clinical trial study with HCRU outcomes				
Dabbous et al. [132]	2020	Value of onasemnogene abeparvovec in spinal muscular atrophy type 1: improvements in motor function, ventilation-free survival, and hospitalizations	–	Open label
Systematic literature review				
Dangouloff et al. [133]	2020	Systematic literature review of the economic burden and economic evaluations in spinal muscular atrophy	–	Systematic literature review

CADTH Canadian Agency for Drugs and Technologies in Health, *HRCU* health care resource utilization, *HTA* health technology assessment, *ICER* Institute for Clinical and Economic Review, *NHS* National Health Service, *NICE* National Institute for Health and Care Excellence, *SMA* spinal muscular atrophy, *SMC* Scottish Medicines Consortium
[a]HTA documents not available in English

associated change in any domain of HRQOL by parental assessment. Of 33 included patients, 22 reported PedsQL values at baseline, 17 reported values at 6 months, and 16 reported values at 12 months. Patient-reported physical function demonstrated statistically significant deterioration at 12 months, with study authors concluding that VPA + L-carnitine failed to improve HRQOL.

Systematic Literature Review of Clinical Efficacy and Safety

Study Selection and Overview

Figure 3 presents the PRISMA flow diagram of the study selection process for the search to identify RCTs and single-arm trials of interest for the SLR of clinical efficacy and safety. This review identified 16 single-arm studies, 11 RCT studies, and five dose-escalation studies (Table 12) [10, 46, 48–50, 52, 63, 71–97], which assessed a variety of therapies for SMA. Patient characteristics across the 32 included studies are

summarized in Table 13 [10, 46, 48–50, 52, 63, 71–97]. Among the 13 included studies with exclusively presymptomatic patients or those with SMA type 1, age at study onset ranged from a median of 19 days in NURTURE [84, 85] to a mean of 9.3 months in Russman et al. [87]. For the 14 included studies with patients with exclusively SMA types 2 and 3, median age at study onset ranged from approximately 4.4 months in Darras et al. [73] to 16.6 years in Chen et al. [71].

Treatments

The therapeutic interventions evaluated in published literature have changed over time with the advent of new treatments such as nusinersen, onasemnogene abeparvovec, and risdiplam. Of the included studies, nine reported nusinersen regimens, six investigated onasemnogene abeparvovec, four assessed VPA, three evaluated risdiplam, and two evaluated olesoxime and salbutamol; hydroxyurea, riluzole, branaplam, somatropin, 4-aminopyridine, and reldesemtiv were each evaluated in one study. Interventions evaluated in trials published in the last 2 years include gene therapy, antisense oligonucleotides, small-molecule therapies, and neuroprotective therapies [98].

Outcome Reporting

The outcomes reported were broadly consistent for SMA types across the included studies. However, scales and measures used to assess these outcomes varied across studies. Motor function was assessed in patients with SMA type 1 using measures explicitly indicated for infants, such as the CHOP INTEND, Hammersmith Infant Neurological Examination-Part 2 (HINE-2), and Test of Infant Motor Performance Screening Items. Ventilator use was only measured in studies of patients with SMA type 1, and forced vital capacity was only measured for patients with SMA types 2, 3, or 4. Quality assessments of the studies are contained in the Supplementary Material.

Systematic Literature Review of Economic Burden

Study Selection and Overview

Figure 4 presents the PRISMA flow diagram of the study selection process for the search to identify studies of interest in the SLR of economic burden. The final list of included studies and publications is presented in Table 14 [55, 59, 61, 62, 65, 69, 99–134]. Among the 42 included studies on economic burden, 20 were cost analyses that reported on the cost of illness. In addition, 20 were full economic evaluations that modeled the cost-effectiveness or cost utility of treatments for SMA; of these, seven were reported in documentation supporting either submissions to or recommendations from health technology assessment (HTA) organizations. Finally, among the remaining two studies, one was a clinical trial that reported health care resource utilization outcomes, whereas another was an SLR of economic burden and economic evaluations in SMA (Dangouloff et al. [133]). A systematic review of the literature identified 13 published full economic evaluations of SMA therapy. Six evaluations compared nusinersen with onasemnogene abeparvovec, five compared nusinersen with the standard of care or BSC, one compared onasemnogene abeparvovec versus BSC, and one compared both onasemnogene abeparvovec and nusinersen with BSC.

Cost Outcomes

Dangouloff et al. [133] reviewed studies evaluating the cost of SMA and economic evaluations of SMA therapies, including original articles published between January 1, 1998, and March 2020. Seven cost analyses and five economic evaluations were included. Cost outcomes reported by economic burden studies were adjusted to 2021 US dollars. The reported annual burden associated with untreated SMA type 1 ranged from $106,000 to $140,000 ($108,704–$143,571 2021 USD) versus $23,000 to $115,000 ($23,587–$117,933 2021 USD) for SMA types 2 to 4. In addition, the reported incremental cost-effectiveness ratios (ICERs) associated with novel therapies (i.e., nusinersen

and onasemnogene abeparvovec) were generally > $200,000 versus no treatment. Because Dangouloff et al. [133] was a conference abstract, the list of included studies was not provided.

Costs

The literature review identified 20 published cost analyses. Ten studies were conducted in the United States, two in Canada, three in Spain, one in Australia, one in Germany, one in Turkey, one in the United Kingdom, and one in Europe (United Kingdom, France, and Germany). The year of costing to address inflation was reported by most of the studies. In general, studies did not clearly state whether costing was based on top-down or micro-costing, except for Chambers et al. [102].

In cost-effectiveness analyses, treatment with onasemnogene abeparvovec and nusinersen produced greater improvements in terms of quality-adjusted life-years (QALYs) compared with BSC, but these improved outcomes were also associated with greater total cost [65, 119]. Moreover, onasemnogene abeparvovec was cost-effective versus nusinersen in all included studies comparing these two treatments [62, 131].

Ali et al. [99] conducted a single-center retrospective analysis based on medical records of all children within the West Midlands, UK. Patients with SMA type 1 who were treated with nusinersen at the Royal Stoke University Hospital were observed to investigate the respiratory care, hospital utilization, and costs associated with newly treated SMA type 1 [99]. Eleven children who received nusinersen between May 2017 and April 2019 were enrolled in this study. The total number of hospital days since diagnosis was 1101, with a median of 118 (range 7–235) days per child, which included general pediatric ward days (median 0, range 0–63), more dependency unit days (median 79, range 7–173), and pediatric intensive care unit days (median 13, range 0–109) per child. This equated to a median of 20% (range 2–72) of their lives in the hospital, and the total cost of the hospital days for these 11 children was £2.2 M ($2.9 M 2021 USD).

Patients with SMA type 1 who were treated with nusinersen initially spend a considerable percentage of their early life in a hospital and have significant ongoing medical costs in addition to the cost of treatment received. Limitations of Ali et al. [99] are that the study includes only 11 patients treated at one center, which questions its representativeness; the retrospective nature of the study may have introduced bias; and the author did not adjust for such potential confounding factors as socioeconomic status and comorbidities.

All other cost-effectiveness data were extracted from seven HTAs: three from HTA agencies in the United Kingdom (one each from the UK's NICE [19], the National Centre for Pharmacoeconomics Ireland [130], and the Scottish Medicines Consortium [126]), one from the Canadian Agency for Drugs and Technologies in Health [127], one from Croatia's Agency for the Quality and Accreditation in Health Care and Social Welfare [128], one from the Swedish Dental and Pharmaceutical Benefits Agency [129], and one from the Institute for Clinical and Economic Review [131].

Malone et al. [61] developed a multi-state survival Markov model over a lifetime to assess the ICER of onasemnogene abeparvovec versus nusinersen in patients with SMA type 1 in the United States. Undiscounted total QALYs per patient were 30.3 for onasemnogene abeparvovec and 7.2 for nusinersen, whereas the discounted (at 3%) QALYs were 15.9 and 5.3, respectively. The estimated discounted lifetime costs were $6.33 M for nusinersen, while the lifetime discounted costs for onasemnogene abeparvovec at hypothetical price points from $2 M to $3 M per dose ranged from $3.7 M to $4.7 M per patient, resulting in cost savings and QALY gains compared with nusinersen. In a scenario analysis in which sitting patients who received gene therapy experienced the survival trajectory of walking patients, onasemnogene abeparvovec undiscounted QALYs were 57.5 (if discounted at 3%: 21.9) and onasemnogene abeparvovec again overshadowed nusinersen at a price of $3 M. The author further suggested that US-based decision-makers should also consider undiscounted QALY gain when assessing the value of innovative therapies because discounting QALYs at the US standard rate of 3% results in a substantial underestimate

of health benefits. Reporting of study methods and results was limited to a single meeting abstract and key information, such as cost year, which was not always provided.

In the same year, Malone et al. [62] revised the Markov model and added more details in this full-text publication. Similar to the above, the objective was to investigate the cost-effectiveness of onasemnogene abeparvovec gene replacement therapy for SMA type 1 compared with nusinersen from the perspective of a commercial insurer in the United States. All costs were reported in 2018 USD based on a lifetime horizon. Survival, health care costs, and QALYs were estimated using natural history data for patients with SMA who achieved motor milestones, whereas health utility weights were obtained from the CHERISH trial [2, 51].

In the base case scenario [61], expected survival (undiscounted) over a lifetime predicted by the model was 37.20 life years for onasemnogene abeparvovec and 9.68 for nusinersen (undiscounted QALYs were 29.86 and 7.21, whereas discounted QALYs were 15.65 and 5.29, respectively). Using a potential onasemnogene abeparvovec price range ($2.5–5.0 M per treatment) and a discount rate of 3%, the estimated mean lifetime cost per patient was $4.2 M to 6.6 M for onasemnogene abeparvovec and $6.3 M for nusinersen. These costs were primarily driven by therapy treatment costs (i.e., the percentage of total costs ranging from 57 to 73% for onasemnogene abeparvovec and 70.9% for nusinersen). The ICER range was –$203,072 to $31,379 per QALY gained for onasemnogene abeparvovec versus nusinersen, indicating that onasemnogene abeparvovec was cost-effective when treatment costs are ≤$5 M. If patients treated with onasemnogene abeparvovec experienced a treatment waning and subsequent loss of milestones at 10 and 25 years, there would be a substantial impact on the survival outcomes (discounted QALYs of 7.80 and 12.95, respectively) and a corresponding reduction in lifetime medical costs. At a price of $5 M for onasemnogene abeparvovec, the estimated lifetime payer cost would be $6.2 M, assuming a 10-year duration of effect and $6.6 M assuming a 25-year duration of effect. Given that the estimated cost of lifetime nusinersen treatment is $6.3 M, onasemnogene abeparvovec dominates nusinersen, assuming a 10-year duration of effect, and generates an ICER of $30,926, assuming a 25-year duration of effect.

With the assumption that treated patients who sit have a normal mortality trajectory, the optimistic survival scenario would be the ICER increased to $57,261 because sitting patients incurred costs of care for longer durations, while the total QALY gain by onasemnogene abeparvovec over nusinersen increased to 16.19. The undiscounted QALYs may be as great as 56.35 years, and the cost per QALY gain for onasemnogene abeparvovec versus nusinersen is $18,864 ($14,347 for base case) [61]. Quality assessments of the studies are given in the Supplementary Material.

DISCUSSION

Natural History

To focus our natural history SLR on the high-quality evidence published to date, we limited the observational evidence base to prospective studies with at least 12 months of follow-up only. However, some studies excluded for retrospective study design or insufficient follow-up may have presented data that would also further our understanding of the natural history of SMA. Because of the heterogeneous nature of the disease, some important endpoints may not be prospectively and consistently collected in the real-world setting. For natural history studies, the majority of included studies focused on children with SMA. In addition, survival outcomes were prospectively reported for patients with SMA type 1 only. Natural history studies prospectively reporting survival outcomes for patients with other types of SMA are warranted. Event-free survival, ventilation support, and nutritional support were prospectively reported by a limited number of studies. More evidence is needed to better understand the clinical course of SMA for these measures.

HRQOL and Utilities

The systematic review of humanistic burden identified studies with authors who concluded that symptomatic SMA corresponded to a strong deterioration in HRQOL for both patients and caregivers. Lower HRQOL was generally associated with the worse clinical phenotype. With the exception of those in the nusinersen 9-mg treatment arm in Chiriboga et al. [52], none of the treatments evaluated in the included trials demonstrated a significant improvement in HRQOL.

Overall, there are limited studies assessing the impact on HRQOL of patients. Health-related quality of life for both patients and their caregivers could be substantially affected by the disease. However, only a small percentage of studies assessed both patients and caregivers, and the majority of the studies focused on patients only. Future studies assessing the impact on caregivers or both patients and caregivers are warranted.

Clinical Efficacy and Safety

The systematic review of clinical efficacy and safety found 32 studies that evaluated various interventions, including conventional treatments and, more recently, DMTs in SMA. The included studies had considerable heterogeneity with respect to baseline patient characteristics, particularly age at diagnosis and study onset. Reported outcomes were broadly consistent for studies, including different SMA types, however, with varied scales or measurement tools to assess these outcomes. Studies with patients who were exclusively presymptomatic or had SMA type 1 generally reported motor function, ventilator use, and survival. Included studies with only patients with SMA types 2 and 3 generally reported motor function. Some of the included studies also evaluated muscle strength and respiratory outcomes, with most reporting adverse events. Varied scales and measures used to assess the outcomes across studies preclude a quantitative synthesis of existing evidence.

Humanistic and Economic Burden

Based on the available data, SMA is associated with substantial humanistic and economic burden. SMA cost data are plentiful, in both magnitude and treatments or resources for which they are available. However, comparisons of cost estimates across studies were hindered by differences in study methodology, choice of the associated time frame, and limitations inherent in the data. We observed large variations in attributable costs as well as in the drivers of costs. The economic costs of SMA are greater for direct medical costs to health care providers, non-medical costs incurred by patients and their caregivers, and indirect costs through productivity losses among informal caregivers. Costs also vary over the trajectory of the condition and are dependent on disease manifestation, progression, and duration of survival. To date, however, a limited number of economic evaluations of interventions for SMA have been published, and the cost-effectiveness of novel SMA therapies has not been conclusively established. Existing literature reported heterogeneous cost-effectiveness ratios and interpreted these ratios based upon different willingness-to-pay thresholds of what constitutes an acceptable threshold in varied settings. However, treatment with both onasemnogene abeparvovec and nusinersen produced larger QALY gains compared with BSC, but these improved outcomes were also associated with greater total costs. In addition, onasemnogene abeparvovec was cost-effective compared with nusinersen in all studies that evaluated these two treatments.

Although the literature suggests that the greater economic costs of SMA are consistent across different health care systems, the economic burden could be reduced by expanding newborn screening and early treatment for SMA [135]. In the future, broader elements of value beyond health gains directly related to treatment should be considered by using QALYs or greater cost-effectiveness thresholds. The use of cost-benefit analyses and saved young life equivalents could be used as an alternative to QALYs for the valuation of outcomes of gene replacement therapies because they use broader

elements of value and avoid the challenges of eliciting utilities for pediatric diseases [136].

Additional Studies

Although this SLR captured a large volume of published literature on SMA treatments, there are some additional studies that should be acknowledged, many of which were published after the completion of our literature searches and some that were not returned in the search results, particularly studies related to DMTs.

In the NICE report published in July 2021 [137], after the SLR search was completed, the committee recommended onasemnogene abeparvovec as an option for treating 5q SMA with a biallelic mutation in the *SMN1* gene and a clinical diagnosis of SMA type 1 in infants ≤6 months of age or 7–12 months of age. Because of the limited trial data for infants aged 7–12 months, their treatment should be discussed by a national multidisciplinary team. The treatment was only recommended for these two groups when permanent ventilation >16 h per day or a tracheostomy was not needed. Onasemnogene abeparvovec was recommended by NICE as an option for treating presymptomatic 5q SMA with a biallelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene in infants [137].

In the EMBRACE study, which evaluated nusinersen in infants and children with infantile- or later-onset SMA (n = 20), motor-milestone responder rates were greater in those receiving nusinersen (93%) versus those receiving sham treatment (29%) [138]. In the NUTURE study, De Vivo et al. [84] found substantial clinical benefit as a result of early initiation of nusinersen treatment in infants with two or three copies of the *SMN2* gene (n = 15; considered most likely to develop SMA type 1 or 2).

New data from RESTORE [135, 139], a comprehensive registry of patients with SMA, were recently presented. In a conference poster, older patients with SMA aged ≥6 months at onasemnogene abeparvovec infusion benefited from treatment as measured by CHOP INTEND and HINE-2 scores. Another poster on the RESTORE registry demonstrated that newborn screening for patients with SMA was associated with significantly earlier diagnosis and intervention and generally achieving motor milestones at earlier ages than clinically diagnosed patients. Compared with those clinically diagnosed, patients who were diagnosed via newborn screening were less likely to receive more than one treatment for SMA.

In the absence of RCTs and head-to-head comparisons, a recent matching-adjusted indirect comparison [140] of patients from START [12], STR1VE-US [13], and SHINE [63, 88] studies demonstrated that treatment with onasemnogene abeparvovec provided significantly greater event-free survival compared with nusinersen for patients with SMA type 1. Patients treated with onasemnogene abeparvovec had numerically longer overall survival compared with nusinersen, although this result was not significant.

Results from the SUNFISH part 2 [141] study, a Phase III, randomized, double-blind, placebo-controlled study, have been recently published. Patients (N = 180) aged 2–25 years with confirmed 5q autosomal recessive SMA type 2 or type 3 were stratified by age and randomly assigned (2:1) to receive either daily oral risdiplam, at a dosage of 5.00 mg (for individuals weighing ≥20 kg) or 0.25 mg/kg (for individuals weighing <20 kg), or daily oral placebo. Treatment with risdiplam resulted in a significant improvement in motor function compared with placebo for patients aged 2–25 years with type 2 or non-ambulant SMA type 3. The exploratory subgroup analyses demonstrated that motor function was generally improved for younger patients and stabilized for older ones. These data require confirmation in further studies.

Some limitations are applicable to all reviews and should be acknowledged. As with any SLR, the evidence base continues to evolve. As such, recently published clinical trials may not have been captured because the searches were conducted up to and including November 2020. Therefore, an update to these SLRs to avoid potential bias as the evidence base evolves would be beneficial. Retrospective analyses and/or prospective studies with cross-sectional data

can be informative, and the exclusion of these studies is another limitation of this study.

There is a risk of publication bias as some clinical trials were published as full-text articles while others were not, presenting limited information. To mitigate the risk, the current study encompassed an extensive search of conference abstracts, gray literature, and clinical trial registries, although studies from these sources do not always provide complete information. As such, studies identified from these sources should be interpreted with caution as they do not undergo the same peer-review process as fully published studies.

Cost data included in the economic review were derived from a heterogeneous set of studies that used varied methodologies. This lack of a standard method for collecting the cost data may impact some of our findings. Also, the included studies were conducted in different countries with various health care systems, which may limit the transferability and comparability of results.

CONCLUSIONS

In conclusion, our SLRs demonstrate substantial methodological heterogeneity between studies in the large volume of recent literature on SMA and, in particular, DMTs for SMA. We conclude that opportunities for synthesis (and thus the ability to reach overarching conclusions on the relative efficacy and safety of different interventions) are limited. The various interventions evaluated in SMA clinical trials reflect a changing therapeutic landscape in which DMTs have only recently been developed and approved. Without conducting a quantitative synthesis, further conclusions cannot be drawn about the relative efficacy and safety of different interventions.

Overall, this review has highlighted a clear need for up-to-date and methodologically rigorous clinical, HRQOL, and economic data to support unbiased assessments of the cost-effectiveness of future SMA treatments. More research is required to extend our understanding of the impact of SMA on HRQOL utility assessments and the impact of new DMTs on HRQOL and utilities for patients with SMA.

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