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PEER-REVIEWED SUMMARY WITH CRITICAL APPRAISAL

Nusinersen for Adolescents and Adults with Spinal Muscular Atrophy: A Review of Clinical Effectiveness

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Abbreviations

95%CI	95% confidence interval
6MWT	6-minute walk test
10MWT	10-minute walk test
ALSFRS	Amyotrophic Lateral Sclerosis Functional Rating Scale
CADTH	Canadian Agency for Drugs and Technologies in Health
CDEC	CADTH drug experts committee
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
FVC	Forced Vital Capacity
HFMSE	Hammersmith Functional Motor Scale Expanded
RCT	randomized controlled trial
RULM	Revised Upper Limb Measure
SD	standard deviation
SMA	spinal muscular atrophy
SMAFRS	Spinal Muscular Atrophy Functional Rating Scale
SMN2	survival motor neuron 2 gene
SR	Systematic Review
US	United States

Context and Policy Issues

Spinal Muscular Atrophy (SMA) is a neuromuscular disorder characterized by the degeneration of alpha motor neurons in the anterior horn of the spinal cord, which leads to progressive weakness of the muscles.[1,2] The majority of SMA cases (95%) are due to an autosomal recessive disorder caused by homozygous deletion and/or mutation of the alleles of the survival motor neuron 1 (SMN1) gene, causing deficiency in the survival motor neuron protein.[3,4] A second set of genes, SMN2, is able to produce small amounts of the SMN protein.[3,4] The number of available SMN2 gene copies and the extent of the expression of these genes modulate the severity of the disease.[1-3]

Nusinersen (Spinraza) has Health Canada's approval for the treatment of 5q SMA. Nusinersen is an antisense oligonucleotide that binds to the SMN2 pre-messenger ribonucleic acid, this leads to increasing the proportion of exon 7 in SMN2 messenger ribonucleic acid transcripts, which ultimately is translated into functional SMN protein.[5] Nusinersen is administered via intrathecal injections of 12 mg in 5 mL solution at day 0, 14, 28, and 63, then given at four month intervals.[5]

Nusinersen was reviewed through the CADTH Common Drug Review originally in 2017 and as a resubmission in 2019. On February 20, 2019, the CADTH Canadian Drug Expert Committee (CDEC) issued a recommendation to reimburse nusinersen for the treatment of 5q SMA if patients met the following conditions:

1. Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote.
2. Patients who:
    a. are pre-symptomatic with two or three copies of SMN2, or
    b. have had disease duration of less than six months, two copies of SMN2, and symptom onset after the first week after birth and on or before seven months of age, or
    c. are 12 years of age or younger with symptom onset after six months of age, and never achieved the ability to walk independently.
3. Patient is not currently requiring permanent invasive ventilation.[6]

The CADTH CDEC recommendation identified the effectiveness of nusinersen treatment in patients older than 12 years of age as an evidence gap. The health technology assessment report that was the basis of this CDEC recommendation included two abstracts of descriptive case series of adult patients treated with nusinersen. However, these two abstracts did not provide sufficient information regarding the study design, patient information, or clinical outcomes, and could not be used as valid sources to inform on the potential effectiveness or safety of nusinersen in adolescent and adult patients with SMA.[7] Since then, new studies examining nusinersen treatment in adult patients with SMA have been published.

The aim of this Rapid Response is to provide a peer-reviewed summary with critical appraisal of the recent evidence on the clinical effectiveness of nusinersen for the treatment of adult and adolescent patients with SMA who are older than 12 years of age.

Research Question

What is the clinical effectiveness of nusinersen in adolescents and adults with spinal muscular atrophy?

Key Findings

Five observational descriptive studies were included in this report. Four of the included observational studies had relatively small sample sizes ranging from six patients to 19 patients. One of the observational studies had a larger sample size (total of 172 patients enrolled), but only provided an analysis at month 14 for 57 patients. Overall, these studies indicated improvements were reflected in the Hammersmith Functional Motor Scale Expanded score, to a lesser extent on the Revised Upper Limb Module score, and mixed scores of improvements, stabilization, and decline in the 6-Minute Walk Test across the studies. Safety was reported in two of the included studies with three events registered as severe.

Limitations of the available evidence revolve around the study design and missing data. The study design (observational and uncontrolled) prevents any sort of statistical inference to be made from the generally small samples within the studies. In addition, several biases are likely to have had an effect in favour of nusinersen, including: selection bias, expectation bias, and attrition bias.

The review cannot answer the question of the clinical effectiveness of nusinersen in adolescent and adult patients with SMA because of the significant limitations of the included studies. The included evidence serves as exploratory information for the formulation of a scientific hypothesis to be tested within a controlled clinical trial study design.

Methods

Literature Search Methods

This report is an update of a literature search strategy developed for a previous CADTH report.[7] For the current report, a limited literature search was conducted on key resources including Medline, Embase, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were nusinersen or Spinraza. No filters were applied to limit the retrieval by study type. The initial search was limited to English-language documents published between January 1, 2016 and May 21, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adolescents and adults aged 13 years and older with spinal muscular atrophy
Intervention	Nusinersen
Comparator	Onasemnogene abeparvovec, best supportive care, placebo or sham, no therapy, no comparator (single-group studies)
Outcomes	Clinical effectiveness: overall survival, need for ventilation, hospital admission, pulmonary function, neuromuscular functioning (e.g., mobility, gross motor function, muscle strength), health-related quality of life, safety
Study Designs	Health technology assessments, Systematic Reviews, Randomized Controlled Trials, Non-Randomized Studies

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, or published prior to 2016. Systematic reviews (SRs) in which all relevant studies were captured in other more recent or more comprehensive systematic

reviews were also excluded. Primary studies were excluded if they were captured in one or more included SRs.

Critical Appraisal of Individual Studies

Critical appraisal of included publication was conducted by one reviewer. The critical appraisal used the following assessment tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2) for systematic reviews,[8] and the Downs and Black Checklist for primary clinical studies.[9] The strength and limitations of the included studies were described narratively rather than provided with a summary score.

Summary of Evidence

Quantity of Research Available

A total of 373 citations were identified in the literature search. Following screening of titles and abstracts, 348 citations were excluded and 25 potentially relevant reports from the electronic search were retrieved for full-text review. Of these potentially relevant articles, 20 publications were excluded for various reasons, and five publications met the inclusion criteria and were included in this report. These comprised five observational studies.[10-14] Appendix 1 presents the PRISMA[15] flowchart of the study selection.

Summary of Study Characteristics

All five included studies were of an observational non-comparative design. Two studies were conducted in the United States (US), two in Germany, and one in Italy. Overall, four of the included five studies specifically addressed the patient population of interest (adolescent or adult patients with SMA).[10-13] Of these, three studies only enrolled adult patients.[10,12,13] The two remaining studies included adolescent or adult patients as a subgroup within the general patient population.[7,14] All of the included studies provided nusinersen treatment as per the regimen described in the product monograph. The most commonly reported outcomes were the Hammersmith Functional Motor Scale Expanded (HFMSE), the Revised Upper Limb Measure (RULM), and the 6-minute walk test (6MWT).

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Three of the primary clinical studies (Hagenacker et al., Yeo et al., and Walter et al.) were of a prospective, observational, non-comparative, cohort study design.[10,12,13] Of these studies, Hagenacker et al. provided uncontrolled before-after statistical analysis.[10] These studies were all published in 2020.

One study, Veerapandiyan et al., published in 2019, was a retrospective, cross sectional, observational, descriptive study of SMA patients 12 years and older from the medical records of a single centre.[11]

One study, Pane et al., published in 2018, was a post-hoc analysis of patients enrolled in the expanded access program for nusinersen.[14] This program enrolled patients who were not eligible to participate in nusinersen trials. Most of the patients enrolled in the program were infants and children, with few adolescents.

Country of Origin

Hagenacker et al. and Walter et al. were conducted in Germany.[10,13] Veerapandiya et al. and Yeo et al. were conducted in the US.[11,12] Pane et al was conducted in Italy.[14]

Patient Population

The patient population in Yeo et al. consisted of six adult patients of a median age of 29.9 years (range 24.9 to 56.5) with SMA type 3. Five patients (83%) were male and one-half had three copies of SMN2. Four (66.7%) of these patients were ambulatory at enrollment with a baseline median 6MWT of 249 meters (range 74 to 429). Other patient characteristics included a median HFMSE score of 35 (range 21 to 53), and a median RULM score of 31.5 (range 22 to 37).[12]

The patient population in Veerapandiyan et al. consisted of 12 adolescent and adult patients, with a mean age of 22 years (range 12 to 52). One-half of patients (50%) were male and seven (58.3%) were classified as having SMA type 3. Three (25%) of these patients were ambulatory at enrollment. The study reported that at baseline the mean RULM score was 14.7 (SD 9.9). No other baseline patient characteristics were available.[11]

In Hagenacker et al., characteristics of enrolled patients were available for three groups based on the duration of follow-up: a 6-month analysis set that included 124 patients, a 10-month analysis set that included 92 patients, and a 14-month analysis set that included 57 patients. In the largest set, 54% were males, this proportion increased to 58% in the 10-months analysis set, and to 65% in the 14-month analysis set. Mean age at treatment initiation was 36 years, 37 years, and 33 years in the 6-month, 10-month, and 14-month analysis set, respectively. In the 6-month analysis set, 39% of patients had 3 copies of SMN2, this decreased to 36% in the 10-month analysis set, and 37% in the 14-months analysis set. SMA type 3 represented 62% of patients in the 6-months analysis set, 65% in the 10-month analysis set, and 65% in the 14-month analysis set. Ambulant patients represented 37% of the 6-month analysis set, 38%, and 40% of the 10-month and 14-month analysis set, respectively. Baseline HFMSE score was the worst in the 6-month analyses set, with a mean of 20.74 (SD 21.39) contrasted with the 10-month analysis set value of 22.95 (SD 21.66) and the 14-month value of 24.65 (SD 21.83). A similar trend appears in the RULM score, where the mean score in the 6-month analysis set was 20.87 (SD 13.27), contrasted with the 10-month analysis set value of 23.00 (SD 12.80) and the 14-month value of 23.85 (SD 12.16). Following the same trend, baseline 6MWT had a mean score of 321.76 (SD217.66) in the 6-month analysis set, contrasted with 353.03 (SD 218.46) and 371.43 (SD 210.34) in the 10-month and 14-month analysis set, respectively.[10]

Walter et al. enrolled a total of 19 adult patients with a mean age of 27.75 years (SD 4.27), of whom 15 (79%) had 4 copies of SMN2 and 7 (37%) were females. Twelve (63%) of these patients were ambulatory at enrollment with a baseline median 6MWT of 369.50 meters (SD 126.62). The baseline mean HFMSE score was 35.16 (SD 21.14), and the baseline median RULM score was 32.32 (SD 7.39).[13]

The study by Pane et al. encompassed all patients that were enrolled in the expanded access program for nusinersen in Italy. This group of patients was mostly infants and adults except for 10 patients that were adolescents. However, the study did not provide baseline characteristics specific to the enrolled adolescents patients.[14]

Further details regarding the population of each included study can be found in Appendix 2.

Interventions and Comparators

All included studies administered nusinersen as the intervention, and none of the studies had a comparator. The dosage and regimen of nusinersen administration was not explicitly outlined in Pane et al.[7,14] The other studies administered nusinersen as per the instructions in the product monograph.[10-13] Information regarding concomitant and supportive therapy or previous history of treatments was not provided.

Outcomes

Three outcomes were most commonly reported across the included studies. These were:

- **The Hammersmith Functional Motor Scale – Expanded (HFMSE)**

  Hammersmith Functional Motor Scale Expanded (HFMSE) is designed to measure motor function in SMA type 2 and 3 diagnosed patients who have limited mobility. It includes 13 items from the Gross Motor Function Measure for patients with cerebral palsy. HFMSE consists of 33 activities with a maximum score of 66, where higher scores represent better motor functions.[16] It has been proposed that an increase of more than two points in the total scores is highly unlikely in untreated SMA type 2 and 3 patients, and maybe considered as a minimum important difference.[17] However, no formal method of establishing a minimum important difference was found in the literature.

- **Revised Upper Limb Module (RULM)**

  The RULM is designed to capture the motor function of the upper limbs in non-ambulatory patients diagnosed with SMA. The revised version was developed to avoid a ceiling effect that was a limitation in the original upper limb module. The scale consists of 19 items and has a maximum score of 37; higher scores represent better upper motor function.[18] Yeo et al. and Hagenacker et al. considered changes of 2 points in the RULM as clinically meaningful based on a study that observed mean changes of -0.45 (SD 2.93) in a 12 month period in 114 SMA type 2 and 3 diagnosed patients who had a mean age of 13.3 years (SD 10.1).[10,12,19] However, no formal method of establishing a minimum important difference was found in the literature.

- **6-minute walk test (6MWT)**

  The 6-minute walk test measures the distance a patient can walk within 6 minutes. The test has been examined in a group of 30 patients with SMA who are ambulatory with a mean age of 23.7 years (SD 16.4).[20] The study showed that the 6MWT is an appropriate test to administer to ambulatory patients diagnosed with SMA and suggested a minimum detectable change (change that is unlikely to be due to measurement error) of 24 meters. The study did not provide a minimum important difference but suggested that in other chronic conditions a minimum important difference of 23 to 45 meters has been defined.[20]

Other outcomes that were not reported consistently across studies included: the spinal muscular atrophy functional rating scale (SMARFS), which is a 10-question scale of various daily activities with a total score of 40 representing total independence; the 10MWT, which is similar to 6MWT with the distance covered measured during 10 minutes as opposed to 6

minutes; and the PedsQL, which is a measure of pediatric health-related quality of life, where higher scores reflect better quality of life for the patient.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Included Primary Clinical Studies

The following critical appraisal points are applicable to all the included primary clinical studies:

- Observational descriptive design: Observational study designs are generally not able to provide causal inference regarding an intervention. Furthermore, the descriptive nature of the studies limits the ability to assess correlation and the ability to make statistical inferences.
- Not clear if a protocol was developed a priori for any of the included studies: The lack of a pre-specified protocol decreases the overall quality of the studies as it becomes unclear whether the outcomes were driven by the data and if there are any selective reporting of the outcomes.
- Lack of a well formulated hypothesis testing statement: The lack of a testable hypothesis renders the included studies as exploratory in nature. Exploratory studies are used to generate hypotheses that can be tested in comparative study designs.
- Lack of a control: The lack of a comparator arm(s) severely limits the usability of the available data as there is no way to account for potential treatment effect modifiers. Any changes observed in a non-comparative study cannot be attributed to the intervention with certainty.
- Lack of random sampling: for a valid statistical inference of a sample into the general population, the sample needs to have been selected through a random method from the population or it should encompass the full population.
- Lack of blinding of intervention or the outcome: The knowledge of the intervention by the participants of the study (patients, investigators, outcome assessors) will lead to an increase in expectations bias.
- Lack of methods for handling missing data: Missing data due to loss of follow-up or any other reason must be accounted for to reduce the risk of attrition bias. Attrition bias usually leads to a bias in favour of the intervention as patients who do not do well on the intervention tend to withdraw from the study.

In addition, four of the included studies (Yeo et al., Veerapandiyan et al., Walter et al., and Pane et al.) had a small sample size, which increases the probability that the sample is potentially not representative of the population.[11-14] Pane et al. also did not provide baseline characteristics of the included patients and reports the outcomes using the CHOP-INTEND outcomes tool, which is designed to measure motor function and development in infants and may not be suitable for the age group of patients over 12 years of age.[14]

Hagenacker et al. enrolled a relatively larger sample size than the other studies (total of 172 patients enrolled), provided baseline characteristics of the included patients, and provided clear and well-defined outcomes at 6 months, 10 months, and 14 months. However, in addition to the limitations associated with the observational, before-after study design and the lack of a comparator group, the study reported a large attrition as a total of 172 patients were enrolled and only 57 (33.14%) patients were analyzed at the final endpoint assessment at month 14. The reason for the 66.86% loss to follow-up is not clearly explained despite the authors providing a flow diagram of the study; some patients were excluded from the analysis despite reaching an assessment milestone with no explanation given as to why they were excluded. No method for handling missing data was described by the authors.[10]

Across the included studies, there were variations on the baseline characteristics relevant to potential treatment effect modifying factors, such as age, proportion ambulatory, number of SMN2, and baseline functional scores. This further complicates our ability to understand the potential effect of nusinersen in adolescent and adult patients.

Summary of Findings

Additional details regarding the results of included publications are provided in Appendix 4.

Clinical effectiveness of nusinersen in adolescent and adult patients with SMA

The Hammersmith Functional Motor Scale – Expanded

Yeo et al. reported that over the course of the study (at various points until 21 months), three (50%) patients improved with greater than 2 points.[12] Walter et al. reported an increase in the mean HFMSE score over the course of study; at baseline, the mean HFMSE score for the 19 enrolled patients was 36.84 (SD 20.65), and at day 300, the mean HFMSE score was 39.50 (SD 20.58).[13] Hagenacker et al. reported the largest HFMSE mean difference from baseline at 14 months in a total of 57 patients. The mean HFMSE difference at 14 months was 3.12 (95%CI 2.06 to 4.19).[10]

Revised Upper Limb Module

Yeo et al. reported that over the course of the study (at various points until 21 months), two (33%) patients improved with greater than 2 points.[12] Veerapandiyan et al. reported that, in a total of 12 patients, the RULM score improved from a mean score of 14.7 (SD 9.9) at baseline to 17.6 (SD 9.3) at last follow up (mean follow-up duration of 17.4 months).[11] Walter et al. reported an increase in the mean RULM score over the course of study; at baseline, the mean RULM score for the 19 enrolled patients was 32.32 (SD 7.39), and at day 300, the mean RULM score was 33.06 (SD 7.33).[13] Hagenacker et al. reported the largest RULM mean difference from baseline at 14 months in a total of 57 patients. The mean RULM difference at 14 months was 1.09 (95%CI 0.62 to 1.55).[10]

6-Minute Walk Test

Yeo et al. reported that two patients had a stable 6MWT results and two patients experienced a decline in the 6MWT over the course of the study (at various points until 21 months).[12] Veerapandiyan et al. reported that results for the 6MWT was available for one patient who experienced an improvement from 18 meters at baseline to 75 meters at 25 months.[11] Walter et al. reported an increase in the mean 6MWT score over the course of study; from 369.50 (SD 126.2) at baseline, to 377.75 (SD 156.60) at day 300.[13] Hagenacker et al. reported the largest 6MWT mean difference from baseline at 14 months in a total of

25 patients. The mean 6MWT difference at 14 months was 46.0 meters (95%CI 25.4 to 66.6).[10]

Other efficacy outcomes

Yeo et al. reported a decline in the SMARF total score and no changes in the PedsQL.[12] Walter et al. reported an increase in the ALSFRS score from 32.17 (SD 4.94) at baseline in 19 patients, to a mean score of 33.07 (SD 5.56) at day 300. Also, Walter et al. reported an increase in the FVC[%] from 94.54 (SD 15.45) at baseline to 99.54 (SD 12.42) at day 300.[13] Pane et al. reported that, out of the ten patients older than 12 years, one patients had a CHOP-INTEND score change at 6 months of 16 points, one patient of 3 points, one of 2 points, one of 1 point, and six patients had no change.[14]

Safety of nusinersen in adolescent and adult patients with SMA

Two of the included studies reported on safety outcomes: Yeo et al. reported a total of 12 adverse events, of which three were severe. Severe adverse events were two recurrent pressure sores and one fall-related injury.[12] Hagenacker et al. reported that, of 172 patients that received at least one nusinersen injection, a total of 82 (47%) patients experienced at least one adverse event. No serious adverse events were reported.[10]

Limitations

The main limitation of the review is the limited evidence base – in terms of quantity of studies and robustness of the findings – and resulting uncertainty in the effects of nusinersen in adolescents and adults with SMA. A key limitation with the included studies is the choice of the study design: the observational and non-comparative nature of the included studies precludes drawing concrete conclusions regarding the effectiveness of nusinersen from the results of the studies. The study designs used do not allow one to conclude that improvements in outcome measures are solely due to nusinersen. The results should be considered descriptive, exploratory, and used to form a scientific hypothesis to be tested in a controlled study design.

The reader should consider the role of selection bias and the resulting confounding by indication which directs patients to a certain intervention. In the case of adult patients with SMA, it is possible that patients who are likely to benefit from the medication or possess certain factors that makes them more likely to receive the treatment have overall better prognosis than patients with advanced stage of the disease. It is not clear if the study samples are representative of the adolescent and adult patient population or if there are any socioeconomic factors at play that may present barriers to access to nusinersen and may have predetermined a subset of patients available for these observational studies. It is acknowledged that SMA is a rare disease and identifying sufficient numbers of patients, especially older patients (adolescents and adults) for interventional studies is a practical limitation. Acknowledging this, however, does not mitigate the likelihood of the impacts of selection bias and the need for a controlled clinical trial.

In addition, the role of expectation bias and the extra support and care provided to the patients during the administration and frequent follow-ups may cause improvements unrelated to the intervention.[21,22]

Another potential source of bias that may play in favour of the intervention is the lack of handling missing data combined with the large percentage of patients lost to follow-up in

the largest included study, Hagenacker et al., is likely to have overestimated the true effect of the intervention in the study population.

These three sources of bias (selection bias, expectation bias, and attrition bias) are all likely to affect the results of the studies in favour of nusinersen.

Conclusions and Implications for Decision or Policy Making

Five observational descriptive studies were included in this report.[10-14] Four of the included observational studies had relatively small sample sizes ranging from six patients to 19 patients. Three of these studies indicated improved functioning based on the HFMSE score, to a lesser extent on the RULM score, and mixed scores of improvements, stabilization, and decline in the 6MWT.[11-13] One study provided the change at six months in the CHOP-INTEND score which is designed for capturing infant motor function and development and may not be an appropriate measure for patients over the age of 12 years.[14]

One study, Hagenacker et al. enrolled a relatively larger sample size (total of 172 patients enrolled). However, this study suffered from a large percentage of patients lost-to-follow up, with a 6-month analysis set that included 124 patients, a 10-month analysis set that included 92 patients, and a 14-month analysis set that included 57 patients. Hagenacker et al. reported the mean HFMSE difference from baseline at 14 months at 3.12 (95%CI 2.06 to 4.19), the mean difference in the RULM score from baseline at 14 months at 1.09 (95%CI 0.62 to 1.55), and the 6MWT mean difference from baseline at 14 months in a total of 25 patients at 46.0 meters (95%CI 25.4 to 66.6).[10]

Safety was reported in two of the included studies; Yeo et al. reported a total of 12 adverse events, of which three were severe. Severe adverse events were two recurrent pressure sores and one fall-related injury.[12] Hagenacker et al. reported that, of 172 patients that received at least one nusinersen injection, a total of 82 (47%) patients experienced at least one adverse event. No serious adverse events were reported.[10]

Limitations of the available evidence revolve around the study design and the lack of addressing missing data. The study design prevents making statistical inferences from the samples within the studies. In addition, several biases, including attrition bias, are likely to have had an effect in favour of the intervention.

Although the results of the included studies suggest a benefit of treatment with nusinersen in adolescent and adult patients with SMA, the findings should serve as the basis of a scientific hypothesis development to be tested within a controlled study design. The lack of comparative evidence of the efficacy and safety of nusinersen in adolescents and adults with SMA population remains an evidence gap that hinders an informative decision-making process regarding the suitability of nusinersen treatment in this age group.

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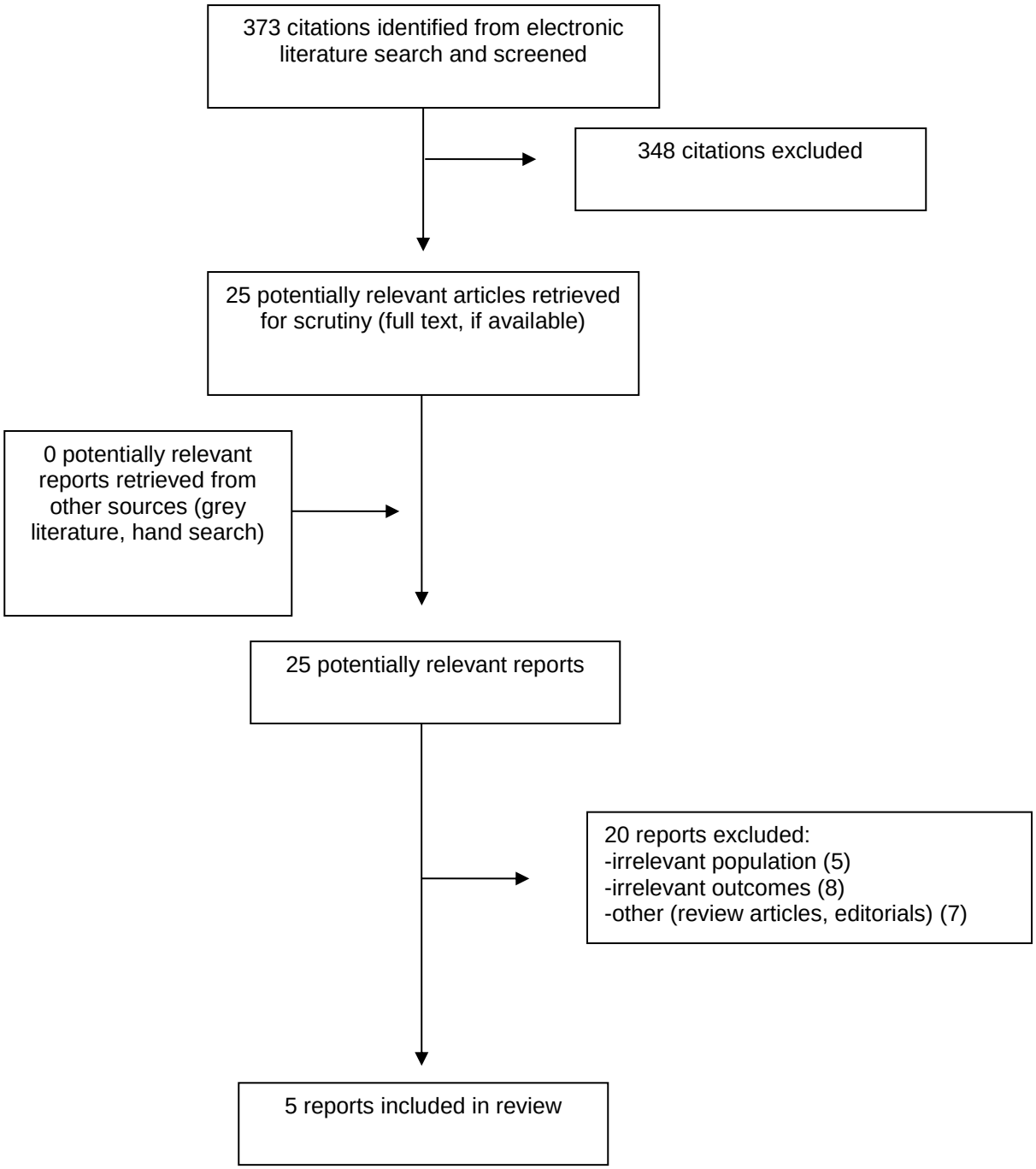
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Yeo, 2020, US	Prospective, observational, non-comparative, cohort/case series study of adult patients with SMA treated with nusinersen treatment.	• Six adults with SMA type 3. • 5 (83%) males • 1 (17%) female • 3 (50%) with three copies of SMN2 • 2 (33%) with four copies of SMN2 • 1 (17%) with five copies of SMN2 • 4 (67%) ambulatory • median age: 29.9 years (range 24.9 to 56.5) • median age at disease onset: 8 years (range 1 to 14) • median baseline HFMSE score: 35 (range 21 to 53) • median baseline RULM score: 31.5 (range 22 to 37) • median baseline 6MWT: 249 (range 74 to 429) • median baseline 10MWT: 10 (range 6 to 19) • median baseline modified SMAFRS: 31.5 (range 21 to 37) • median baseline PedsQL Multidimensional Fatigue Scale: 58 (range 43 to 68)	• Nusinersen (Spinraza) as per indication • No comparator	• HFMSE, RULM, 6MWT, 10MWT, SMAFRS, PedsQL, and safety. • The study had a mean follow-up duration of 17 months (range 14 to 21)
Veerapandiyan, 2020, US	Retrospective, cross-sectional study of hospital records of patients 12 years and older diagnosed with SMA and received nusinersen treatment	• 12 patients • Ages were 12, 14, 16, 17, 19, 25, 47, and 52 years • Mean age at first dose: 22 years (range 12 to 52) • 6 females, 6 males • One patient classified as SMA type 1	• Nusinersen (Spinraza) as per indication • No comparator	• RULM, 6MWT. • The study had a mean follow-up duration of 17.4 months (range 4 to 26)

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		• Four patients classified as SMA type 2 • Seven patients classified as SMA type 3 • Three patients ambulatory • At baseline, the mean RULM score was 14.7 (SD 9.9)		
Hagenacker, 2020, Germany	Prospective, observational, non-comparative, cohort/case series study of adult patients with SMA treated with nusinersen treatment.	• 124 patients included in the 6 months analysis set • 92 patients included in the 10 months analysis set • 57 patients included in the 14 months analysis set • 57 (46%) of the patients in the 6 months analysis set were females • Mean age in the 6 months analysis set was 36 years (SD 12) • 7 (6%) with two copies of SMN2 in the 6 months analysis set • 48 (39%) with three copies of SMN2 in the 6 months analysis set • 41 (33%) with four copies of SMN2 in the 6 months analysis set • 2 (2%) with five copies of SMN2 in the 6 months analysis set • 2 (2%) with six copies of SMN2 in the 6 months analysis set • 24 (19%) with unknown SMN2 copies number in the 6 months analysis set • 46 (37%) ambulatory in the 6 months analysis set • Mean baseline HFMSE score in the 6 months	• Nusinersen (Spinraza) as per indication • No comparator	• HFMSE, RULM, 6MWT. • 124 patients had a follow-up duration of 6 months • 92 patients had a follow-up duration of 10 months • 57 patients had a follow-up duration of 14 months.

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		analysis set: 20.74 (SD 21.39) • Mean baseline RULM score in the 6 months analysis set: 20.87 (SD 13.27) • Mean baseline 6MWT score in the 6 months analysis set: 321.76 (SD 217.66)		
Walter, 2019, Germany	Prospective, observational, non-comparative, cohort/case series study of adult patients with SMA treated with nusinersen treatment.	• 19 patients • 4 (21%) with 3 copies of SMN2 • 15 (79%) with 4 copies of SMN2 • 7 (37%) female • 12 (63%) ambulatory • Mean age at start of therapy: 27.75 years (SD 4.27) • Mean age of onset: 8 years (SD 7.12) • Mean duration of disease: 19.75 years (SD 10.05) • Mean HFMSE score: 35.16 (SD 21.14) • Mean RULM score: 32.32 (SD 7.39) • Mean 6MWT: 369.50 (126.62) • Mean ALSFRS score: 32.17 (SD 4.49) • Mean percentage of FVC: 94.54 (SD 15.45)	• Nusinersen (Spinraza) as per indication • No comparator	• HFMSE, RULM, 6MWT, ALSFRS, and FVC. • Did not report on mean duration of follow-up. However, the authors report that out of the 19 patients, 2 withdrew their consent before visit 4 (day 63). The last endpoint for outcome was reported on visit 6 (day 300)
Pane, 2018, Italy	A post-hoc analysis of patients with SMA type enrolled in the expanded access program for nusinersen. These patients were ineligible to participate in nusinsersen trials and include various age groups and SMA clinical presentations	• 10 patients older than 12 years had results available at 6 months assessment • No baseline characteristics available specifically for these patients	• Nusinersen (Spinraza) Dosage and regimen unclear • No comparator	CHOP-INTEND

6MWT= 6-minute walk test; 10MWT= 10-minute walk test; ALSFRS = Amyotrophic Lateral Sclerosis Functional Rating Scale; CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; FVC = Forced Vital Capacity; HFMSE =Hammersmith Functional Motor Scale Expanded; RCT = randomized controlled trial; RULM = Revised Upper Limb Measure; SD = standard deviation; SMA = spinal muscular atrophy; SMAFRS = Spinal Muscular Atrophy Functional Rating Scale; SMN2 = survival motor neuron 2 gene; US = United States.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Clinical Studies using Downs and Black scale[9]

Strengths	Limitations
Yeo, 2020[12]	
• Clearly described objectives. • Clearly described outcome measures. • Patients characteristics clearly outlined. • Clearly described intervention. • Clearly described findings. • Treatment settings and intervention are representative of the treatment of the population. • Considering the nature of the intervention, compliance with the intervention is not considered a potential issue.	• Lacks a clearly described statement of a hypothesis to be tested. • Lack of control group. • Lack of blinding, of intervention and outcomes. • Does not report if any patients were lost to follow-up. • Did not report if study was planned a priori, and whether a protocol existed. • Does not provide statistical analysis of outcomes. • Method of identifying and selecting patients is not reported. • Small sample size. **Additional notes by the reviewer:** With the lack of random sampling, control group, statistical analysis, and the small sample size, no valid inference can be made from the results of this study to the SMA adult population. Readers should consider the existence of selection bias, expectation bias, and potential confounders when considering the results of this study.
Veerapandiyan, 2020[11]	
• Clearly described objectives. • Clearly described outcome measures. • Patients characteristics clearly outlined. • Clearly described intervention. • Clearly described findings. • Treatment settings and intervention are representative of the treatment of the population. • Considering the nature of the intervention, compliance with the intervention is not considered a potential issue. • Describes the follow-up duration for each enrolled patient.	• Lack of a clearly described statement of a hypothesis to be tested. • Lack of control group. • Lack of blinding, of intervention and outcomes. • Did not report if a protocol existed or was developed a priori. • Does not provide statistical analysis of outcomes. • Method of identifying and selecting patients is not a random sampling of the population. • Small sample size. **Additional notes by the reviewer:** With the lack of random sampling, control group, statistical analysis, and the small sample size, no valid inference can be made from the results of this study to the SMA adult population. Readers should consider the existence of selection bias, expectation bias, and potential confounders when considering the results of this study.
Hagenacker, 2020[10]	
• Clearly described objectives. • Clearly described outcome measures. • Patients characteristics clearly outlined. • Clearly described intervention. • Clearly described findings. • Treatment settings and intervention are representative of the treatment of the population. • Considering the nature of the intervention, compliance with the intervention is not considered a potential issue.	• Lack of a clearly described statement of a hypothesis to be tested. • Lack of control group. • Lack of blinding, of intervention and outcomes. • Sampling method is not a random selection from SMA adult population. • Did not report if a protocol existed or was developed a priori. • Does not provide the characteristics of patients who were lost to follow-up.

Strengths	Limitations
• Provides the number of patients at each analysis visit. • Multi-centre study (10 centres), • Sample size is relatively large compared to other studies in the field.	• Statistical analysis does not account for lost to follow-up. • Method of identifying and selecting patients is not a random sampling of the population. **Additional notes by the reviewer:** With the lack of random sampling and a control group, statistical inferences can not be made from the results of this study. The authors included only patients that are undergoing nusinersen treatment, no control group or a description of the characteristics of patients who are not receiving nusinersen treatment was provided. As such, we cannot assess the extent of selection bias and the resulting effect of confounding by indication. Moreover, considering that the study enrolled 172 patients and only assessed 57 patients at 14 months, there is a high probability of attrition bias. This large percentage of patients lost to follow-up combined with the lack of applying any method of handling missing data would lead to biased results in favour of the intervention. Readers should consider the existence of selection bias, expectation bias, attrition bias, and potential confounders when considering the results of this study.
Walter, 2019[13]	
• Clearly described objectives. • Clearly described outcome measures. • Patients characteristics clearly outlined. • Clearly described intervention. • Clearly described findings. • Treatment settings and intervention are representative of the treatment of the population. • Considering the nature of the intervention, compliance with the intervention is not considered a potential issue. • Describes the number of patients lost to follow-up	• Lack of a clearly described statement of a hypothesis to be tested. • Lack of control group. • Lack of blinding, of intervention and outcomes. • Sampling method is not a random selection from SMA adult population. • Did not report if a protocol existed or was developed a priori. • Does not provide the characteristics of patients who were lost to follow-up. • Statistical analysis does not account for lost to follow-up. • Method of identifying and selecting patients is not a random sampling of the population. **Additional notes by the reviewer:** With the lack of random sampling, a control group, and the small sample size statistical inferences can not be made from the results of this study. Readers should consider the existence of selection bias, expectation bias, attrition bias, and potential confounders when considering the results of this study.
Pane, 2018[14]	
• Clearly described objectives. • Clearly described outcome measures. • Clearly described intervention. • Clearly described findings. • Treatment settings and intervention are representative of the treatment of the population.	• Lack of a clearly described statement of a hypothesis to be tested. • Lack of control group. • Lack of blinding, of intervention and outcomes. • Post-hoc analysis. • Lacks description of baseline characteristics.

Strengths	Limitations
• Considering the nature of the intervention, compliance with the intervention is not considered a potential issue. • Describes the number of patients lost to follow-up	• Outcome measure not appropriate for the population of interest. **Additional notes by the reviewer:** The reported outcome measure in this study is the CHOP-INTEND score. This score is designed to measure motor function in infants and children with neuromuscular disorders. As such, this score may not be an appropriate reflection of the clinical status of adult patients with SMA.

CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SMA = spinal muscular atrophy.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Yeo, 2020[12]	
• Results were available for a total of 6 patients, 4 of whom were ambulatory. • The authors provided a visual presentation of each patient's change in HFMSE and RULM score at various points. • Over the course of the study (21 months), 3 (50%) of patients had an HFMSE score change greater than 2 points and none of the patients had a negative change. • Mean HFMSE score change was 2 points (range 1 to 5). • A RULM score change greater than 2 points was reported in 2 (33%) patients. and none of the patients had a negative change. • Mean RULM score change was 1.8 points (range 0 to 3). • 6MWT was reported as stable and in two patients and declining in two other patients. • 10MWT was reported as stable in three patients and increasing in one patient. • SMAFRS total score showed a decline in all but one patient. • PedsQL showed little changes in most patients. • A total of 12 adverse events were recorded: 6 mild, 3 moderate, and 3 severe. Severe adverse events were 2 recurrent pressure sores and 1 fall-related injury.	"HFMSE and RULM show potential as responsive outcome measures of motor function in ambulatory and non-ambulatory adults with SMA type 3. A time-dependent accrual of benefit of nusinersen on motor function was apparent in this cohort. More sensitive alternative measures of quality of life, fatigue, exercise tolerance, stability and ADLs are clearly needed for adults with SMA".[12]
Veerapandiyan, 2020[11]	
• Results were available for a total of 12 patients at baseline and after loading doses, and for 10 patients after the first and second maintenance dose. Three patients were ambulatory. • At baseline, the mean RULM score was 14.7 (SD 9.9). • After loading doses, the mean RULM was 16.8 (SD 9.3). • At last follow-up (the study had a mean follow-up duration of 17.4 months), the mean RULM was 17.6 (SD 8.9). • Results for the 6MWT was available for one patient: 18 meters at baseline, 37.5 meters after loading dose, and 75 meters at 25 months.	"Intrathecal nusinersen can be safely delivered in older SMA patients. Available functional outcome measures are not adequate to capture meaningful subjective Improvements".[11]
Hagenacker, 2020[10]	
• At 6 months, the HFMSE mean difference from baseline for 124 patients was 1.73 (95%CI 1.05 to 2.41). • At 6 months, the RULM mean difference from baseline for 120 patients was 0.66 (95%CI 0.26 to 1.05). • At 6 months, the 6MWT mean difference from baseline for 47 patients was 22.1 meters (95%CI 8.7 to 35.6). • At 10 months, the HFMSE mean difference from baseline for 92 patients was 2.58 (95%CI 1.76 to 3.39). • At 10 months, the RULM mean difference from baseline for 90 patients was 0.59 (95%CI 0.15 to 1.03). • At 10 months, the 6MWT mean difference from baseline for 37 patients was 31.1 meters (95%CI 15.2 to 47.1).	"Despite the limitations of the observational study design and a slow functional decline throughout the natural disease course, our data provide evidence for the safety and efficacy of nusinersen in the treatment of adults with 5q spinal muscular atrophy, with clinically meaningful improvements in motor function in a real-world cohort".[10]

Main Study Findings	Authors' Conclusion
• At 14 months, the HFMSE mean difference from baseline for 57 patients was 3.12 (95%CI 2.06 to 4.19). • At 14 months, the RULM mean difference from baseline for 58 patients was 1.09 (95%CI 0.62 to 1.55). • At 14 months, the 6MWT mean difference from baseline for 25 patients was 46.0 meters (95%CI 25.4 to 66.6). • Of 172 patients that received at least one nusinersen injection, a total of 82 (47%) patients experienced at least one adverse event	
Walter, 2019[13]	
• At Baseline, the mean RULM score for 19 patients was 32.32 (SD 7.39). • At day 63, the mean RULM score was 32.58 (SD 7.31). • At day 180, the mean RULM score was 32.76 (SD 7.31). • At day 300, the mean RULM score was 33.06 (SD 7.33). • At Baseline, the mean HFMSE score for 19 patients was 35.16 (SD 21.14). • At day 63, the mean HFMSE score was 36.84 (SD 20.65). • At day 180, the mean HFMSE score was 38.59 (SD 20.13). • At day 300, the mean HFMSE score was 39.50 (SD 20.58). • At Baseline, the mean 6MWT score for 19 patients was 369.50 (SD 126.2). • At day 63, the mean 6MWT score was 384.73 (SD 131.80). • At day 180, the mean 6MWT score was 378.83 (SD 147.17). • At day 300, the mean 6MWT score was 377.75 (SD 156.60). • At Baseline, the mean ALSFRS score for 19 patients was 32.17 (SD 4.94). • At day 63, the mean ALSFRS score was 32.65 (SD 4.68). • At day 180, the mean ALSFRS score was 32.57 (SD 5.58). • At day 300, the mean ALSFRS score was 33.07 (SD 5.56). • At Baseline, the mean FVC [%] for 19 patients was 94.54 (SD 15.45). • At day 63, the mean FVC [%] was 96.31 (SD 16.50). • At day 180, the mean FVC [%] was 98.52 (SD 14.48). • At day 300, the mean FVC [%] was 99.54 (SD 12.42).	"This prospective observational study indicates a mild treatment effect in adults with long-standing SMA3 after 10 months of treatment with Nusinersen, which had never occurred in the natural history of the disease. In our cohort, the most significant outcome measures were the 6MWT with statistically significant changes after day 180 and day 300, RULM after day 300 and peak cough flow after day 180".[13]
Pane, 2018[14]	
• As most of the study population were children, the study provided outcomes description using the CHOP-INTEND measure. • At the assessment point of six months, a total of 10 patients were 12 years or older. Of these, one had a CHOP-INTEND change of 16 points, one of 3 points, one of 2 points, one of 1 point, and the rest of these patients had 0 change in their CHOP-INTEND score.	"Our preliminary results suggest that functional improvement can be observed in type 1 patients outside the range of the inclusion criteria used in the Endear study".[14]

6MWT= 6-minute walk test; 10MWT= 6-minute walk test; ALSFRS = Amyotrophic Lateral Sclerosis Functional Rating Scale; CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; FVC = Forced Vital Capacity; HFMSE =Hammersmith Functional Motor Scale Expanded; RCT = randomized controlled trial; RULM = Revised Upper Limb Measure; SD = standard deviation; SMA = spinal muscular atrophy; SMAFRS = Spinal Muscular Atrophy Functional Rating Scale; SMN2 = survival motor neuron 2 gene; US = United States.