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Key statement

Research question

The objective of this investigation is to assess the benefit of newborn screening for 5q-linked spinal muscular atrophy (SMA). In the process, newborn screening for 5q-linked SMA in combination with earlier diagnosis and therapy is assessed in comparison with no 5q-linked SMA screening with regard to patient-relevant outcomes.

Conclusion

No comparative interventional studies of the screening chain were available for the comparison of newborn screening for 5q-linked SMA versus no newborn screening. Therefore, interventional studies permitting the comparison of an earlier versus later treatment start as well as studies on diagnostic quality were used and combined by means of the linked evidence approach.

For the **comparison of an early versus late symptomatic treatment start**, 1 small randomized controlled study with a short follow-up period can be used; it examined drug therapy in comparison with a sham procedure in children with infantile 5q-linked SMA. For the combined outcome of time to death or permanent ventilation as well as for the outcome of motor milestone achievement, subgroup analyses revealed effect differences between children with an early symptomatic treatment start (disease duration $\leq$ 12 weeks) and children with a later treatment start (disease duration > 12 weeks). For both outcomes, children benefit more from an early symptomatic treatment start than from a late symptomatic treatment start. The outcomes of serious adverse events, severe adverse events, and treatment discontinuation due to adverse events each showed no effect differences between subgroups. For other outcomes, no usable data were available.

For the **comparison of a presymptomatic versus an early symptomatic treatment start**, 1 small retrospective comparative study, which was made available by the manufacturer upon request, was included. Data were available on children with diagnosed 5q-linked SMA and 2 survival motor neuron (*SMN)2* copies (i.e. prognosis or confirmation of infantile SMA). For the outcome of motor milestone achievement, large effects were found in favour of a presymptomatic treatment start over early symptomatic treatment start (disease duration $\leq$ 12 weeks); these effects were not explicable solely by bias (dramatic effect). For the outcomes of serious adverse events and severe adverse events, statistically significant differences were found in favour of a presymptomatic treatment start. These observed differences were assessed as small enough to be explicable solely by the effect of confounders. For each of the outcomes of overall survival, permanent ventilation, treatment discontinuation due to AEs, and back pain, no statistically significant differences were found. The criteria of a dramatic effect were not met. No data were requested on other outcomes.

It was not possible to include any comparative interventional studies on **patients with a later disease onset than in the infantile form**.

For the assessment of **diagnostic quality**, it was possible to include 4 studies, but these studies verified only positive test results (verification-of-only-positive-testers design). The results of these studies suggest that the examined test methods are suitable for newborn screening for 5q-linked SMA. It remains unclear how many affected children were missed by the testing.

In summary, there is an indication of benefit of newborn screening for 5q-linked SMA when compared with no screening. This result is based, first, on data on the presymptomatic, early symptomatic, and late symptomatic drug treatment of children with diagnosed 5q-linked SMA and a prognosis or confirmation of the infantile form. The included data show an association between timing and effect according to which an earlier treatment start is associated with better treatment results. Second, the derivation of an indication of benefit of newborn screening is based on the suitability of diagnostic test methods and the opportunity to achieve an earlier diagnosis (and hence treatment) by means of newborn screening. The available data do not permit drawing any conclusions as to whether children identified by the screening to have late-onset SMA (i.e. symptom onset not until years later) would benefit from a presymptomatic treatment start. Currently, it is therefore especially unclear how to handle newborns who test positive in the screening and are expected to have late-onset disease (≥ 4 *SMN2* copies). If newborn screening is introduced, it will be essential to consider how to appropriately handle these children and their families – including the option of letting them decide for themselves whether or not they wish to know about the presence of mild courses of SMA forms.

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List of abbreviations

Abbreviation	Meaning
AE	Adverse event
aRQ	Average relative quantity
BSC	Best supportive care
CHOP	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
Cq	Cycle of quantification
ddPCR	Droplet digital polymerase chain reaction
DNA	Deoxyribonucleic acid
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HINE-2	Hammersmith Infant Neurological Examination – Subscale 2
HR	Hazard ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems, Revision 10
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	Intention to treat
MD	Mean difference
MLPA	Multiplex ligation-dependent probe amplification
PCR	Polymerase chain reaction
PPV	Positive predictive value
qPCR	Quantitative real-time polymerase chain reaction
RCT	Randomized controlled trial
RT-PCR	Real-time polymerase chain reaction
SAE	Serious adverse event
SD	Standard deviation
SGB	Sozialgesetzbuch (Social Code Book)
SMA	Spinal muscular atrophy
SMN	Survival motor neuron
SMN1	Survival motor neuron 1
SMN2	Survival motor neuron 2
SOC	System organ class
VOPT	Verification of only positive testers

1 Background

Spinal muscular atrophy (SMA) linked to chromosome 5q is an autosomal recessive genetic disorder. It is rare; its prevalence is reported as 1–2:100 000 [1] and up to 1:30 000 [2, 3], and the incidence of SMA type I is reported to be 1:10 000 [1, 2].

The disorder is characterized by progressive motor neuron degeneration, leading to muscular atrophy and muscle weakness.

Motor neurons are nerve cells that specifically stimulate the muscle, thereby triggering the muscle contraction involved in voluntary movement. The survival of these neurons absolutely requires the survival motor neuron (SMN) protein. This SMN protein is encoded by the *SMN1* gene. Homozygous deletion of both alleles of the *SMN1* gene results in 5q-linked SMA [4, 5]. *SMN2*, the adjacent and very similar gene, also produces functional SMN protein, albeit in lower quantities than the *SMN1* gene. In most cases, the disorder occurs in this homozygous form. However, about 5% of patients have a different genetic abnormality (heterozygous deletion and point mutation on the existing *SMN1* gene) [6–8].

Typical symptoms of 5q-linked SMA include muscle weakness, delayed motor development, and, depending on the type, possibly severe pulmonary dysfunction. The literature discusses 4 types [9], but they cannot be clearly distinguished [10, 11]. The types differ in symptom onset and severity, motor milestones achieved, and number of *SMN2* copies. SMA type I, for instance, is characterized by onset within the first few weeks of life; children fail to learn to sit unaided. Without (supportive) therapy, most of these children die by the age of 1 to 2 years [6, 12, 13]. SMA type II is defined by symptom onset after the 6th month of life. A higher life expectancy is reported for this type [6, 12]; in some cases, it is 10 to 40 years [13]. Children with SMA type II may learn to sit unaided, but they never stand and/or walk unaided [12]. Patients with SMA type III appear to have a normal life expectancy [13]. Patients learn to walk but lose this ability in the course of their lives due to progressive muscular atrophy. Milder forms are considered SMA type IV. SMA type 0 is defined by prenatal symptom onset. From birth, these children require respiratory support to survive [6, 11–14]. On average, the period between symptom onset and diagnosis is 3.6 months for SMA type I, 14.3 months for SMA type II, and 43.6 months for SMA type III [15]. The 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) distinguishes infantile SMA from other inherited SMA [16]. While infantile SMA corresponds to SMA type I, other inherited SMA comprises types II, III, and IV, which are distinguished by age of onset.

Drug therapy of 5q-linked SMA comprises the gene therapeutic insertion of the *SMN1* gene as well as *SMN2* modification. *SMN2* modification is intended to increase the production of functional SMN protein encoded by the *SMN2* gene. This approach has been pursued with the only drug which is currently, since 2017, approved for the treatment of 5q-linked SMA in Germany. Nusinersen is administered intrathecally by lumbar puncture [17, 18]. Another approach involves SMN-independent therapies (such as neuroprotectants). Valproic acid in

children and other SMN-independent treatment strategies are currently being researched (e.g. [19]). In May 2019, the U.S. Food and Drug Administration (FDA) approved the gene replacement therapy AVXS-101 [20] in the USA for children under 2 years. It has not yet been approved in Europe. Multidisciplinary therapy comprises rehabilitative, orthopaedic, and psychological measures, muscle maintenance, and respiratory and nutritional support.

5q-linked SMA can be presymptomatically diagnosed using a blood sample: For this purpose, a test is done for the homozygous *SMN1* gene deletion. In addition, the *SMN2* gene copy number, which is associated with the severity of disease, is determined [11, 22, 23].

Dried blood spots on filter paper cards can be used for SMA diagnostics. The German expanded newborn screening programme performed in accordance with the paediatric guideline of the Federal Joint Committee (G-BA)'s [24] uses a blood sample taken from a vein or the heel in the 36th to 72nd hour of life, which is dripped onto filter paper cards and examined for various diseases. Currently, 5q-linked SMA is not among the diseases tested in the expanded newborn screening.

Newborn screening for 5q-linked SMA aims to achieve earlier diagnosis and treatment of affected children.

2 Research question

The objective of this investigation is to assess the benefit of newborn screening for 5q-linked spinal muscular atrophy (SMA). In the process, newborn screening for 5q-linked SMA in combination with earlier diagnosis and therapy is assessed in comparison with no 5q-linked SMA screening with regard to patient-relevant outcomes.

3 Methods

Comparative studies of the screening chain were included in the benefit assessment. In the event that such studies were not available or were of insufficient quantity or quality, the plan called for an assessment of interventional studies which allow comparing earlier versus later treatment start as well as studies on diagnostic quality as the individual components of the screening chain (linked evidence).

Comparative interventional studies of the screening chain

Newborns were the target population of the benefit assessment. The experimental intervention was newborn screening for 5q-linked SMA in combination with earlier diagnosis and treatment. The comparator intervention was "no screening strategy".

The investigation examined the following patient-relevant outcomes:

- Mortality (overall survival, disease-specific survival),

- Morbidity (e.g. developmental and growth disorders such as motor milestone achievement, hospitalizations, dyspnoea caused by 5q-linked SMA),

- (Serious) Adverse events ([S]AEs)

- Health-related quality of life of the child.

Randomized controlled trials (RCTs) were to be included in the benefit assessment. Whenever the available RCT-based evidence was insufficient for the benefit assessment, non-randomized comparative interventional studies and comparative cohort studies (including retrospective or with historical comparison cohort) were to be included as well. There were no restrictions regarding the study duration.

Comparative interventional studies on treatment start

If no comparative interventional studies of the screening chain were found, the assessment also included interventional studies with patients with 5q-linked SMA which allowed a comparison between earlier versus later nusinersen treatment start. Diagnostics for patients with an early treatment start had to be transferable to the newborn screening situation. For the intervention to be examined, 2 different treatment start points were taken into account: (a) presymptomatic treatment start was considered as the intervention to be examined; (b) earlier treatment start after symptom onset (hereinafter: early symptomatic) was used as the intervention to be examined. The comparator intervention for each of them was later treatment start after symptom onset (hereinafter: [late] symptomatic). The above-mentioned patient-relevant outcomes were to be examined in the investigation. RCTs were included in the assessment. If no RCTs were available on a research question, studies of a lower evidence level (retrospective comparative studies) were included in the benefit assessment. There were no restrictions regarding the study duration.

Studies on diagnostic quality

If earlier treatment start was associated with a benefit (see "Information retrieval, assessment, and synthesis" section), the present report also included studies on diagnostic quality for the benefit assessment. The assessment included studies done with newborns. The index test was testing for 5q-linked SMA using filter paper. The reference test was genetic analyses. In case of negative findings in the index test, follow-up was an acceptable alternative. Studies were included if they provided data suitable for calculating diagnostic quality in terms of the detection of 5q-linked SMA.

Information retrieval, information assessment, and synthesis

A systematic search for studies was conducted in the databases MEDLINE, Embase, and Cochrane Central Register of Controlled Trials. In parallel, a search for relevant systematic reviews was conducted in the databases MEDLINE, Embase, Cochrane Database of Systematic Reviews, and HTA Database.

The following sources of information and search techniques were additionally used: Study registries, queries to manufacturers, publicly accessible documents from regulatory authorities, documents sent by the Federal Joint Committee (G-BA), the G-BA website and IQWiG website, reviews of reference lists, documents made available from hearing procedures, and requests to authors.

Relevant studies were selected by 3 persons independently from one another. The results of the selection were summarized after the full-text assessment. Data were extracted into standardized tables. To assess the qualitative certainty of results, outcome-specific and study-level criteria of the risk of bias were assessed and each rated as high or low. In studies on diagnostic quality, transferability to the German healthcare context was examined in addition to the risk of bias. The results of the individual studies were organized according to outcomes and described.

To the extent that the studies were comparable in terms of their research questions and relevant characteristics and no meaningful heterogeneity was observed, the results from individual studies were to be quantitatively combined in meta-analyses.

For each outcome, a conclusion was drawn on the evidence for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: Proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or neither of the above 3. The latter was the case if no data were available or the available data did not permit classification into one of the 3 other categories. In that case, the conclusion "There is no hint of (greater) benefit or (greater) harm" was drawn. To the extent that this assessment also included RCTs which permitted a comparison between an earlier versus later treatment start by means of subgroup analyses, a favourable conclusion on the benefit of an earlier treatment start was laid out in detail and worded broadly. In this situation, it was possible to draw a favourable conclusion regarding the benefit of an earlier treatment start due to a statistically significant interaction (hint of effect difference depending on treatment start) and the simultaneous

existence of statistically significant treatment effects in favour of the intervention, at least for the group with an earlier treatment start. Drawing conclusions regarding a benefit on the basis of studies of a lower evidence level (retrospective comparative studies) was permissible only if the effects found were too large to be explicable solely by the impact of confounding factors (dramatic effect). The benefit of screening was derived by comparing the health-related consequences of the potential test results and their probabilities in conjunction with a conclusion on the benefit of earlier treatment start (linked evidence approach). In this manner, the reliability of results regarding the benefit of screening took into account both the reliability of results regarding the benefit of an earlier treatment start and regarding diagnostic quality.

4 Results

4.1 Results of the comprehensive information retrieval

The information retrieval found no study on the screening chain to be relevant for the research question of this benefit assessment. No planned or ongoing studies on the screening chain were found. The most recent search for studies on the screening chain took place on 23 October 2019.

The information retrieval found 1 study (14 documents) with data suitable for comparing an early versus late symptomatic treatment start as relevant for the research question of the present benefit assessment. Further, for the comparison of a presymptomatic versus early symptomatic treatment start, data were made available by the manufacturer and included as relevant for the present benefit assessment in the form of 1 retrospective comparative study (1 document). No further planned or ongoing comparative interventional studies on treatment start were found. The most recent search for comparative interventional studies on treatment start took place on 23 October 2019.

The information retrieval found 4 studies (7 documents) on diagnostic quality to be relevant for the research question of this benefit assessment. Three ongoing studies on diagnostic quality were found. The most recent search for studies on diagnostic quality took place on 23 October 2019.

The search strategies for bibliographic databases and trial registries are found in the appendix.

Table 1: Study pool of the benefit assessment

Study	Available documents		
	Full publication (in professional journals)	**Registry entry / results report from the study registries**	**Study report and other documents from manufacturer documents (not publicly accessible)**
Comparative interventional studies of the screening chain			
No studies found			
Comparative interventional studies on treatment start			
Early versus late symptomatic treatment start			
ENDEAR	Yes [25]	Yes [26–30][a] / Yes [31, 32]	Yes [33–37] [38][b]
Presymptomatic versus early symptomatic treatment start			
Biogen 2019	No	No	Yes [39][c]
Studies on diagnostic quality			
Chien 2017	Yes [14]	Yes [40] / no	No
Czibere/Vill 2019	Yes [41, 42] [43][d]	No/no	No
Kariyawasam 2019	Yes [44]	No/no	No
Kraszewski 2018	Yes [45]	No/no	No
a: SHINE is an ongoing study which follows, among others, children who were treated in ENDEAR. Therefore, this report linked the SHINE registry entry [27] with the ENDEAR study. b: Publicly accessible on the G-BA website. c: No full publication for the requested comparison; upon request, data were supplied as part of the commenting procedure of the preliminary report; these are referred to as the Biogen 2019 study. To supplement this information, publications and study reports on the ENDEAR [25, 33] and NURTURE [46, 47] studies were used, e.g. to present details on the intervention. d: No full publication (information sheet without presentation of results). G-BA: Federal Joint Committee			

4.2 Comparative interventional studies of the screening chain

No comparative interventional studies of the screening chain were found. Therefore, the individual components of the screening chain were assessed – both on the basis of comparative interventional studies on treatment start (Section 4.3) and on the basis of studies on diagnostic quality (Section 4.4).

4.3 Comparative interventional studies on treatment start

For the comparison of early versus late symptomatic treatment start, 1 RCT was included in the benefit assessment. For the comparison of presymptomatic versus early symptomatic treatment start, 1 retrospective comparative study was included in the benefit assessment. Both are presented below.

4.3.1 Characteristics of the studies included in the assessment

4.3.1.1 Early versus late symptomatic treatment start

One study with data comparing an early versus late symptomatic treatment start was included (ENDEAR) [33]. The study in question is 1 RCT comparing nusinersen treatment versus a sham procedure in children with infantile 5q-linked SMA. It provided data from prescheduled subgroup analyses on the comparison of an early versus late symptomatic treatment start. In this benefit assessment, this comparison was interpreted with regard to moving up the treatment start. To provide background for these data, first the study context is presented, and then the included subgroups are characterized.

The ENDEAR study

The study was multi-centric with a total of 31 centres in North America, Europe, Asia, and Australia. It included 122 children with early-onset 5q-linked SMA (2 *SMN2* gene copies), i.e. children aged ≤ 6 months at symptom onset and aged ≤ 7 months at study inclusion. The 122 children with infantile SMA were randomly allocated in a 2:1 ratio to nusinersen treatment or sham treatment, stratified by disease duration (≤ 12 or > 12 weeks between the child's age at symptom onset and age at study inclusion). Consent for participation was withdrawn for 1 child; therefore, 121 children were included in the intention-to-treat (ITT) analysis.

In the nusinersen group, children received an age-dependent dose of nusinersen as an intrathecal bolus injection on study days 1, 15, 29, 64 (loading doses) as well as 183 and 302 (maintenance doses). The control group instead received a sham procedure in the form of a needle prick on the lower back (no lumbar puncture) on the corresponding days. In both groups, the children received best supportive care (BSC) as needed.

In total, the children were to be treated for 10 months, with a subsequent 3-month follow-up. However, the study was prematurely terminated after a planned interim analysis due to evidence of efficacy of nusinersen. The mean follow-up at the final data cut-off on 16 December 2016 was 40 weeks (minimum 1, maximum 63) in the nusinersen group and 27 weeks (minimum 3, maximum 60) in the control group. The evidence of efficacy was based on favourable effects of nusinersen therapy for the outcome of motor milestone achievement, which was collected, among others, by means of subscale 2 of the Hammersmith Infant Neurological Examination (HINE-2) and analysed in the form of a responder analysis. This outcome was retroactively defined as a primary outcome of the study. This protocol change was justified by the fact that phase 2 data suggested that a functional response might provide early proof of efficacy and hence enable an earlier interim analysis [38]. The original primary and ultimately co-primary outcome was the combined outcome of time to death or permanent ventilation. This outcome comprised the events of death or permanent ventilation, which was defined as ventilation for ≥ 16 hours per day continuously for > 21 days in the absence of acute reversible events or tracheotomy. Acute reversible events were predefined, and each case was evaluated by a blinded, central, and independent committee (endpoint adjudication committee). Other patient-relevant outcomes included further operationalizations of the outcomes of motor milestone

achievement, developmental and growth disorders, hospitalizations, SAEs, severe AEs, and treatment discontinuations due to AEs. The definition of severe AEs comprised both incapacity and substantial disruption of the ability to conduct normal life functions [33].

In the study, predefined subgroup analyses were conducted, e.g. on disease duration (≤ 12 or > 12 weeks between age at symptom onset and age at study inclusion) [33]. These analyses were used for the comparison of early versus late symptomatic treatment start.

Subgroup analysis relevant for the present assessment from the ENDEAR study

The subgroup with a disease duration of ≤ 12 weeks between symptom onset and study inclusion was used for the experimental intervention of early symptomatic treatment start, while the subgroup with a disease duration > 12 weeks was used for the comparator intervention of late symptomatic treatment start. Related data were requested from the manufacturer, including data on patient characteristics and results on patient-relevant outcomes for these subgroups (see Section A3.1.1.3 of the full report).

The subgroup with early symptomatic treatment start included a total of 52 children (nusinersen n = 34 versus sham treatment n = 18), and the subgroup with late symptomatic treatment start, 69 children (nusinersen n = 46 versus sham treatment n = 23). While the children hardly differed in median age at symptom onset, the mean age at the 1st dose was 16 weeks (range: 7 to 34 weeks) in the subgroup with an early symptomatic treatment start versus 19 weeks (4 to 33 weeks) in the sham treatment group. In the subgroup with late symptomatic treatment start, the age was 28 weeks (18 to 35) versus 30 weeks (20 to 37).

4.3.1.2 Presymptomatic versus early symptomatic treatment start

One retrospective comparative study with data comparing a presymptomatic versus early symptomatic start of nusinersen treatment was included (Biogen 2019) [39]. The manufacturer generated and provided the study upon request (see Section A3.1.1.3 of the full report). In this benefit assessment, this comparison was interpreted with regard to an earlier treatment start.

The Biogen 2019 study's intervention group with presymptomatic treatment start is based on the population of the NURTURE study. The comparator group with early symptomatic treatment start is composed of children from the above-described ENDEAR study. The latter population is thus part of both comparisons undertaken in this report with respect to moving up the start of treatment.

To provide context for the results of the Biogen 2019 study, the following first provides an outline of the NURTURE study. Thereafter, the Biogen 2019 study is described in detail.

The NURTURE study

The NURTURE study is an ongoing, open-label, 1-arm observational study on the pre-symptomatic treatment of SMA with nusinersen; it was conducted as a multi-centric study at a total of 15 sites in 7 countries. Recruitment has already been completed. Planned and included

in accordance with the study protocol were 25 children with genetically confirmed 5q-linked SMA who, at the time of study inclusion, did not yet exhibit any clinical symptoms and were ≤ 6 weeks old. Fifteen children had 2 *SMN2* copies, and 10 children, 3 *SMN2* copies. Hence, the natural history of the disease (i.e. untreated course of disease) for the majority of these children would very likely culminate in an early disease onset (SMA type I or II).

On each of the study days 1, 15, 29, and 64, each of the children received 12 mg nusinersen in the form of an intrathecal bolus injection (loading phase), followed by 1 maintenance dose every 4 months starting from study day 183, for a total period of 5 years. After the last dose, a follow-up evaluation is planned to be done every 3 months. Adequate supportive care is permitted over the course of the study. The most recent data cut-off date of 29 March 2019 comprises all 25 children at a median age of about 34 months.

The primary outcome of the study is the combined outcome of time to death or respiratory intervention, which is defined as invasive or non-invasive ventilation for ≥ 6 hours per day continuously for ≥ 7 days or tracheotomy. Further patient-relevant outcomes include the combined outcome of time to death or permanent ventilation (and its individual components), various operationalizations of the outcome of motor milestone achievement, the development of clinical manifestations of SMA, developmental and growth disorders, hospitalizations due to respiratory events, SAEs, severe AEs, and treatment discontinuations due to AEs. The definition of severe AEs comprised both incapacity and substantial disruption of the ability to conduct normal life functions [46, 47].

The Biogen 2019 study

As requested, the manufacturer supplied separate analyses for 2 target populations: (1) children with 2 *SMN*2 copies and (2) children with 3 *SMN*2 copies. This eliminated any potential structural inequalities concerning this characteristic. However, since the number of included children with 3 *SMN2* copies (6 children with a presymptomatic and 5 with an early symptomatic treatment start) was insufficient for drawing reliable conclusions on the benefit (or harm), these data were deliberately omitted in the report (see appendix, Biogen comment on the preliminary report [39]). The below-stated description of the Biogen 2019 study refers exclusively to the comparison regarding children with 2 *SMN2* copies.

The included Biogen 2019 study is based on data from 49 children who each have 2 *SMN2* copies. Fifteen children received presymptomatic nusinersen treatment as part of the 1-arm NURTURE study. Thirty-four children received early symptomatic nusinersen treatment in the ENDEAR study (see above).

As an inherent part of the underlying research question, the compared populations differ regarding the presence or absence of symptoms at the start of the study. Further, the populations differ in terms of their age at study inclusion in accordance with the inclusion criteria of the underlying NURTURE and ENDEAR studies. Children with a presymptomatic treatment start

were on average 14 weeks younger at study inclusion and were on average treated 15 weeks earlier than children with an early symptomatic treatment start.

To allow an appropriate comparison between the two subpopulations, data were requested not for specific follow-up points as counted from the start of the study, but based on child age (e.g. "age 1 year").

The treatment regimens of the two study arms are sufficiently comparable.

Data were transmitted and presented on the outcomes of overall survival, permanent ventilation, SAEs, severe AEs, treatment discontinuations due to AEs, back pain (as an SAE and severe AE), as well as motor milestone achievement.

4.3.2 Overview of patient-relevant outcomes

Data on patient-relevant outcomes were extracted from 2 studies. Table 2 presents an overview of the available data on patient-relevant outcomes from the included studies.

Table 2: Matrix of patient-relevant outcomes

Study	Mortality/ morbidity	Mortality		Morbidity							QoL
	Time to death or permanent ventilation	Overall survival	Disease-specific survival	Motor milestone achievement	Developmental and growth disorders	Hospitalizations	Dyspnoea	Permanent ventilation	Serious respiratory events	(Serious) AEs	Health-related quality of life
Comparison of early vs. late symptomatic treatment start											
ENDEAR	●[a]	●[b]	-	●[c]	○[d]	○[e]	_[f]	●[g]	○[h]	●[i]	-
Comparison of presymptomatic vs. early symptomatic treatment start											
Biogen 2019	_[j]	●	-	●	_[j]	_[j]	_[j]	●	_[j]	●	-

● Data were reported and were usable.

○ Data were reported but were not usable for the benefit assessment.

- No data were reported (no further information). / Outcome not surveyed.

a: Combined outcome, comprising the individual components of time to death or permanent ventilation, which was defined as ventilation for ≥ 16 hours per day continuously for > 21 days in the absence of acute reversible events or tracheotomy.

b: Outcome taken into account and presented as a subcomponent of the combined outcome of time to death or permanent ventilation. Data on the disease duration subgroups relevant for the report were (in part) taken from documents which are not publicly accessible.

c: Data on the disease duration subgroups relevant for the report were (in part) taken from documents which are not publicly accessible. Regarding the subgroups relevant for the report, results on the CHOP and HINE-2 instruments were available in the form of responder analyses as well as the change in scores from baseline and interaction test results. HINE-2 results in the form of responder analyses were taken into account and presented.

d: The outcome was reported in the form of the operationalizations of HINE-1 and HINE-3. No usable data on disease duration were available for the subgroups relevant for the report.

e: For the disease duration subgroups relevant for the report, only p-values on the interaction test were available. The results were not interpretable, in part due to the absence of patient-based analysis, and were therefore not used.

f: In the study, dyspnoea was recorded as an AE (preferred term). No data were available for the disease duration subgroups relevant for the report.

g: This outcome is taken into account and presented as a subcomponent of the combined outcome of time to death or continuous ventilation. Data on the disease duration subgroups relevant for the report were (in part) taken from documents which are not publicly accessible.

h: The outcome comprises all AEs which occurred during the study period, were rated as serious, and were classified in the system organ class (SOC) of "Respiratory, thoracic and mediastinal disorders" as their primary or secondary SOC. Rare events in the SOCs "Infections and infestations" and "Investigations" (if any) were not taken into account. For the disease duration subgroups relevant for the report, only p-values on the interaction test were available. The results were not interpretable, in part due to the absence of patient-based analysis, and were therefore not used.

i: This includes SAEs, severe AEs as well as discontinuation due to AEs. Data on the disease duration subgroups relevant for the report were (in part) taken from documents which are not publicly accessible.

j: Results on the outcome were not requested.

AE: adverse event; CHOP: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE: Hammersmith Infant Neurological Examination; HINE-1: HINE – subscale 1; HINE-2: HINE – subscale 2; HINE-3: HINE – subscale 3; LQ: health-related quality of life; SAE: serious adverse event; SOC: system organ class

4.3.3   Assessment of the risk of bias of results

4.3.3.1   Early versus late symptomatic treatment start

The risk of bias at study level is assessed as low.

The risk of bias at outcome level was found to be high for the results on the combined outcome of time to death or permanent ventilation, on the outcome of motor milestone achievement, and on the outcomes of SAEs, severe AEs, and treatment discontinuations due to AEs. This is due to the fact that no data were available on the distribution of concomitant treatment between the subgroups. However, since study participants received concomitant treatment in accordance with BSC and the available data on the overall population document a variety of concomitant treatments, corresponding data for the subgroups would have been necessary to assess any potential co-intervention bias. Consequently, the qualitative certainty of results was rated as moderate for all outcomes.

4.3.3.2   Presymptomatic versus early symptomatic treatment start

Due to the retrospective study design, the risk of bias at study level is rated as high. The risk of bias at outcome level was therefore rated as high for all reported outcomes as well, and the qualitative certainty of results was consequently rated as very low for all outcomes.

4.3.4   Results on patient-relevant outcomes

4.3.4.1   Results on the combined outcome of time to death or permanent ventilation

4.3.4.1.1   Early versus late symptomatic treatment start

For the combined outcome of time to death or permanent ventilation, the ENDEAR study provided results on the subgroups relevant for the report. The interaction test showed a statistically significant interaction between the subgroups of early versus late symptomatic treatment start (disease duration ≤ 12 versus > 12 weeks) in children with infantile SMA ($p = 0.008$). The effect in favour of nusinersen in case of an early symptomatic treatment start (HR: 0.16; 95% CI: [0.06; 0.44]; $p < 0.001$) was statistically significant, whereas the difference in case of a late symptomatic treatment start was not statistically significant (HR: 0.82; 95% CI: [0.43; 1.54]; $p = 0.533$).

The individual components exhibited the same direction of effects, with the component of time to permanent ventilation also exhibiting a statistically significant interaction ($p = 0.040$). However, the model used by the study team for calculating the HR differs between this individual component and the combined outcome (HR based on Cox regression versus a priori planned Cox regression, adjusted for disease duration at the time of recruitment). For the individual component of time to death, the interaction was not statistically significant; the effect estimators in the subgroups are comparable with the overall group.

All things considered, for the combined outcome of time to death or permanent ventilation, there is consequently a hint of the existence of different effects based on treatment start in

symptomatic children with infantile SMA, with the effect being statistically significantly in favour of nusinersen for an early symptomatic treatment start.

4.3.4.1.2 Presymptomatic versus early symptomatic treatment start

Results on the combined outcome of time to death or permanent ventilation were not requested from the manufacturer. Results on this outcome were therefore not available for the Biogen 2019 study.

Due to the few events reported for the individual components (see Sections 4.3.4.2.2 and 4.3.4.8.2), the combined outcome is not expected to show a dramatic effect, which, given the study's very low qualitative certainty of results, would need to be demonstrated for a conclusion on benefit.

4.3.4.2   Results on overall survival

4.3.4.2.1   Early versus late symptomatic treatment start

For the outcome of overall survival, usable results from the ENDEAR study were available for the subgroups relevant for the report. This outcome was taken into account and presented as a subcomponent of the combined outcome of time to death or permanent ventilation (see Section 4.3.4.1).

4.3.4.2.2   Presymptomatic versus early symptomatic treatment start

For the outcome of overall survival, the Biogen 2019 study supplied data on the number of deaths.

At the age of 1 year, all 15 children of the intervention group with presymptomatic treatment start were alive. In the comparator group with early symptomatic treatment start, 3 children (9%) had died by that time.

However, this numerical difference in overall survival was not statistically significant. The criteria of a dramatic effect were not met (see General Methods Version 5.0 [48]). On this basis, there is no hint of greater benefit or harm of a presymptomatic versus early symptomatic treatment start for the outcome of overall survival.

4.3.4.3   Results on disease-specific survival

4.3.4.3.1   Early versus late symptomatic treatment start

Regarding the outcome of disease-specific survival, no results on disease duration were available for the subgroups relevant for the report.

4.3.4.3.2 Presymptomatic versus early symptomatic treatment start

Data on the outcome of disease-specific survival were not requested from the manufacturer since no corresponding results were to be expected from the underlying studies ENDEAR and NURTURE.

4.3.4.4 Results on motor milestone achievement

4.3.4.4.1 Early versus late symptomatic treatment start

Regarding the outcome of motor milestone achievement, the ENDEAR study supplied results on the instruments of HINE-2 (for the primary study outcome) and CHOP (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) INTEND in various operationalizations for the subgroups relevant for the report. Neither instrument has been conclusively validated to date. Furthermore, a validated minimal important difference (MID) is not available for the instruments. Nevertheless, HINE-2 was included in the present benefit assessment. In light of the rarity of the disease and the availability of results on the individual items, which are each separately considered patient relevant and can contribute to the interpretation of responders in the total score, HINE-2 was taken into account in the form of responder analyses for the outcome of motor milestone achievement. CHOP INTEND was not presented since it is a different operationalization of the same outcome. The results are in the same direction as those of HINE-2.

HINE-2 results in the form of responder analyses using the total score were taken into account for the subgroups relevant for the report on the basis of the ITT set. Further, results on responder analyses were presented for the collected individual items of HINE-2. They were, however, only available on the basis of the efficacy set (patients followed up to at least study day 183). The definition of total score responders is based on 7 out of 8 individual milestone categories of HINE-2, which are each measured on the basis of scales of 3 to 5 possible development stages. The study team excluded intentional grasping from the responder analyses since this motor milestone is achieved even by many untreated children with SMA. Total score responders were defined as children who met the following criteria: (1) $\geq$ 1-point improvement in the categories of head control, turning, sitting, crawling, standing or walking or $\geq$ 2-point improvement in the category of kicking and/or achievement of the maximum score in the kicking category, (2) more categories with improvement than categories with deterioration. Deceased children and study dropouts were counted as non-responders. Responders for the individual items were defined analogously to the component parts of the total score.

For HINE-2 total score responders, a statistically significant interaction between the subgroups of early versus late symptomatic treatment start (p = 0.003) was found, where children benefited more from early symptomatic versus late symptomatic treatment start. Within each of the subgroups, a statistically significant effect in favour or nusinersen was found (early symptomatic treatment start: RD: 0.71; 95% CI: [0.55; 0.86]; p < 0.001; late symptomatic treatment start: RD: 0.37; 95% CI: [0.23; 0.51]; p = 0.00). There were no responders in the group of children receiving the sham procedure.

The results for the individual items of HINE-2 show that, with the exception of 1 child receiving sham procedure, only children with nusinersen treatment exhibited improvements in the form of being responders regarding individual motor milestones. In addition, numerically, there were more responders across all items in the subgroup with early symptomatic treatment start than in the subgroup with late symptomatic treatment start. Additional data from the study report reveal that these differences are not explicable by dissimilarities in developmental stages at the start of the study because, with few exceptions, the population had not yet started the development process for the various motor milestones at that point. All things considered, these data support the statistically significant result of the interaction test for the total score responder analysis.

On the basis of these results, for the outcome of motor milestone achievement, a hint of different effects based on treatment start is derived for symptomatic children with infantile SMA, with the effect being greater for early symptomatic treatment start than for late symptomatic treatment start.

4.3.4.4.2 Presymptomatic versus early symptomatic treatment start

For the outcome of motor milestone achievement, the Biogen 2019 study provided the following usable data on the HINE-2 instrument: 1.) in the form of a change in total score from study start to the age of 1 year and 2.) in the form of illustrations of the highest levels achieved of the 4 individual items of "sitting: pivots", "crawling: crawling on hands and knees", standing: stands unaided", and "walking: walking independently". The change in HINE-2 total score was based on all 8 milestone categories of HINE-2 (and thereby differs from the HINE-2 responder analyses presented in the above section, which included only 7 of the 8 individual items).

In the intervention group with presymptomatic treatment start, the mean HINE-2 total score at study start was 2.67 points (standard deviation [SD] 1.59), while in the comparator group with early symptomatic treatment start, it was 1.15 points (SD 1.10). At that point, the values of the two groups already differed in a statistically significant way (mean difference [MD]: 1.52; 95% CI: [0.58; 2.46]; p = 0.003). On the one hand, children with early symptomatic treatment start would be expected to have had higher scores at study start since they were about 3 months older at study start than children with presymptomatic treatment start. On the other hand, the lower score achieved by these children can be explained by the presence of symptoms, which might have already led to motor development regression due to the commenced loss or failed development of motor neurons. At the age of 1 year, the mean of the intervention group with presymptomatic treatment start rose to 19.67 (SD 4.15). In the comparator group with early symptomatic treatment start, a rise to a mean of 5.86 points (SD 3.16) was found. Hence, the difference between the two groups at the age of 1 year is larger (MD: 13.81; 95% CI: [11.01; 16.61]; p < 0.001) than the difference between the groups at the start of the study.

The changes in HINE-2 total score from the time of study start to the age of 1 year differ substantially between the groups in favour of presymptomatic treatment start versus early symptomatic treatment start (Hedges' g: 3.62; 95% CI: [2.38; 4.86]). The lower confidence

limit is more than 10 times higher than the typical limit of 0.2 used in clinical relevance assessment (see General Methods 5.0 [48]). This difference is assessed as too large to be explicable solely by the impact of confounding factors.

The graphically depicted results on highest level achievement of the individual items show that in the comparator group with early symptomatic treatment start, with the exception of 1 child who achieved the highest level in the individual item "sitting" at 15 months, none of the children achieved 1 or more of these 4 milestones. In the group with presymptomatic treatment start, in contrast, the highest level of the milestones was achieved by virtually all of the children (sitting), the majority of them (crawling and standing), or some of them (walking). The different treatment and follow-up durations and hence different ages of the groups at the last follow-up partially explain the difference. However, a distinct difference remains even when analysing only children whose response score is available up to the age of about 13 months. On average, that time point is the last follow-up of the comparator group with early symptomatic treatment start. While none of the children of the group with early symptomatic treatment start achieved a milestone at that time point, about half of the children with presymptomatic treatment start were able to pivot while sitting at that time, one-third of the children, to crawl on hands and feet, and 1 child, to stand unaided.

Overall, these data support the result on changes in the HINE-2 total score. All things considered, there is a dramatic effect on the basis of which, for the outcome of motor milestone achievement, a hint of greater benefit is derived for presymptomatic versus early symptomatic treatment start.

4.3.4.5   Results on developmental and growth disorders

4.3.4.5.1   Early versus late symptomatic treatment start

Beyond the outcome of motor milestone achievement, the ENDEAR study collected data on further developmental and growth disorders using the HINE instrument (subscales 1 and 3). No usable data were available with regard to the disease duration subgroups relevant for the report.

4.3.4.5.2   Presymptomatic versus early symptomatic treatment start

Results on the outcome of developmental and growth disorders were not requested from the manufacturer. Consequently, no results on this outcome were available.

4.3.4.6   Results on hospitalizations

4.3.4.6.1   Early versus late symptomatic treatment start

For the outcome of hospitalizations, no usable data from the ENDEAR study were available with regard to the disease duration subgroups relevant for the report (for details, see Section A3.3.2.6 of the full report).

4.3.4.6.2 Presymptomatic versus early symptomatic treatment start

Results on the outcome of hospitalizations were not requested from the manufacturer. Consequently, no results on this outcome were available.

4.3.4.7 Results on dyspnoea

4.3.4.7.1 Early versus late symptomatic treatment start

The outcome of dyspnoea was recorded in the form of AEs in the ENDEAR study. No data were available with regard to the disease duration subgroups relevant for the report.

4.3.4.7.2 Presymptomatic versus early symptomatic treatment start

The outcome of dyspnoea was collected in the form of AEs in the ENDEAR and NURTURE studies, on which Biogen 2019 is based. It was not separately requested from the manufacturer. Consequently, no results on this outcome were available.

4.3.4.8 Results on permanent ventilation

4.3.4.8.1 Early versus late symptomatic treatment start

In the ENDEAR study, the outcome of ventilation was collected in the form of various operationalizations. The present assessment took into account the results on permanent ventilation, which were analysed as a subcomponent of the combined outcome of time to death or permanent ventilation (see Section 4.3.4.1).

4.3.4.8.2 Presymptomatic versus early symptomatic treatment start

For the outcome of permanent ventilation, the Biogen 2019 study supplied usable data on the number of children with events.

At the age of 1 year, none of the children (0%) of the intervention group with presymptomatic treatment start required permanent ventilation. In the comparator group with early symptomatic treatment start, 2 children (6%) received permanent ventilation at that time point.

This difference in permanent ventilation was not statistically significant. The criteria of a dramatic effect were not met (see General Methods Version 5.0 [48]). On this basis, for the outcome of permanent ventilation, there is no hint of greater benefit or harm of presymptomatic versus early symptomatic treatment start.

4.3.4.9 Results on serious respiratory events

4.3.4.9.1 Early versus late symptomatic treatment start

The outcome of serious respiratory events was collected in the ENDEAR study, but no usable data were available with regard to the disease duration subgroups relevant for the report (see Section A3.3.2.9 of the full report).

4.3.4.9.2 Presymptomatic versus early symptomatic treatment start

Results on the outcome of serious respiratory events were not requested from the manufacturer. Nevertheless, results on SAEs are presented in the following section.

4.3.4.10 Results on (serious) adverse events

4.3.4.10.1 Early versus late symptomatic treatment start

For the outcomes of SAEs, severe AEs, and treatment discontinuation due to AEs, the manufacturer sent additional data from the ENDEAR study with regard to the disease duration subgroups relevant for the report. For none of the 3 outcomes did the interaction test show any statistically significant interaction between the subgroups of early versus late symptomatic treatment start (disease duration ≤ 12 / > 12 weeks) in children with infantile SMA.

In both subgroups, the number of children with events were lower in the nusinersen group than in the control group, with the effect being statistically significant for the outcomes of severe AEs and treatment discontinuations due to AEs in the subgroup with early symptomatic treatment start (also see Chapter 5).

Data on individual (S)AEs were not available with regard to the subgroups relevant for the report.

Overall, for the outcomes of SAEs, severe AEs, and treatment discontinuations due to AEs, there is no hint of a difference of effects on the basis of treatment start in symptomatic children with infantile SMA.

4.3.4.10.2 Presymptomatic versus early symptomatic treatment start

For the outcomes of SAEs, severe AEs, treatment discontinuations due to AEs, and back pain (as an SAE and severe AE), usable results were available from the Biogen 2019 study.

For all 4 outcomes, the number of children with events was numerically higher in the comparator group with early symptomatic treatment start than in the intervention group with presymptomatic treatment start. Regarding SAEs and severe AEs, the differences were statistically significant in favour of the group with presymptomatic treatment start. These observed differences are small enough to be explicable solely by the impact of confounding factors. On this basis, for the outcomes of SAEs, severe AEs, treatment discontinuations due to AEs, and back pain (as an SAE and severe AE), there is no hint of greater or lesser harm of a presymptomatic versus early symptomatic treatment start.

4.3.4.11 Results on the child's health-related quality of life

4.3.4.11.1 Early versus late symptomatic treatment start

The included study did not collect any data on the outcome of the child's health-related quality of life.

4.3.4.11.2 Presymptomatic versus early symptomatic treatment start

On the outcome of the child's health-related quality of life, no data were requested from the manufacturer since this outcome was not collected in the ENDEAR study, which is one of the bases of Biogen 2019, and hence no data were available for the subpopulation with early symptomatic treatment start. Consequently, no results on this outcome were available.

4.4 Studies on diagnostic quality

4.4.1 Characteristics of the studies included in the assessment

Four studies on diagnostic quality were included. All of them are prospective diagnostic cohort studies using a verification-of-only-positive-testers (VOPT) design, and no systematic follow-up or reference test is described for those testing negative.

The Chien 2017 [14] prospective diagnostic cohort study describes the results of a newborn screening programme in Taiwan. In the period of November 2014 through September 2016, 120 267 newborns were examined in a consecutive series using dried blood spots. The absence of *SMN1* was to be detected by means of real-time polymerase chain reaction (RT-PCR). For this purpose, a threshold of *SMN1* ΔRn < 1 was defined for positive tests. In case of insufficient quality of the deoxyribonucleic acid (DNA), the test was repeated. In case of positive test results, the same sample material was examined using subsequent droplet digital polymerase chain reaction (ddPCR) in order to confirm and quantify *SMN2* copies. Final positive results were based on this 2-stage screening method. Using multiplex ligation-dependent probe amplification (MLPA) of fresh whole blood, final positive results were then examined for homozygous *SMN1* exon 7 deletion, and the respective number of *SMN2* copies was determined.

The Czibere/Vill 2019 study [41, 42] is an ongoing newborn screening programme conducted in Germany. For the present report, this study serves as a study on diagnostic quality. Since January 2018, the programme has been conducted in the German states of Bavaria and North Rhine-Westphalia, using newborn dried blood spots to detect homozygous deletion of *SMN1* exon 7. According to the authors, this programme covers about 80% of all newborns in Bavaria and about 40% of all newborns in North Rhine-Westphalia [42]. Up to the time of publication of Czibere 2019, tests were performed on 213 279 newborns, and up to the publication of Vill 2019, there were 241 270. Since the latter data were cited by the authors as preliminary results and the publication provides no data on the genetic verification of these preliminary results, the present report uses the data on the 213 279 newborns with verified screening test results from the Czibere 2019 positive testers. The homozygous SMN1 exon 7 deletion was identified using quantitative polymerase chain reaction (qPCR). The *SMN1* gene copy was considered to exist if a product was found before PCR cycle 36 (quantification cycle value, Cq value < 36), while a Cq value < 34 was defined for the amplification of the internal control. If a product was detected only in the control, the test was considered positive, i.e. the newborn likely had a homozygous deletion of *SMN1* exon 7. In that case and in case of invalid test results (i.e. absence of product in both the sample and the control), a new blood spot sample was punched

out, and the test was run again. In an independent laboratory, final test-positive findings were then examined for homozygous *SMN1* exon 7 deletion via MLPA using fresh whole blood, and the respective number of *SMN2* copies was determined by duplicate testing.

The publication on the prospective diagnostic cohort study Kariyawasam 2019 [44] describes results from a newborn screening programme in Australia. From August 2018 through July 2019, it was conducted throughout the state of New South Wales and in the Australian Capital Territory. Dried blood spots from a total of 103 903 newborns were examined. The absence of *SMN1* was to be detected by RT-PCR, but no data on the employed pre-validated threshold was found in the publication. In case of a positive test result, a new dried blood spot was punched out from the filter paper and examined using subsequent ddPCR for confirmation. In addition, the number of *SMN2* copies was determined in this step using the 1st and 2nd sample. Only newborns with < 4 *SMN2* copies were defined as test positive. Individuals with ≥ 4 *SMN2* copies were described as test negative and not reported. This study consequently uses a more narrow definition of the target disease than the 3 other studies included on diagnostic quality. Final positive tests were determined on the basis of the described 2-stage screening and subsequently examined by means of genetic confirmation on fresh whole blood.

The prospective diagnostic cohort study Kariyawasam 2018 [45] describes results from a newborn screening programme in New York State. From January 2016 through January 2017, dried blood spots from 3826 newborns were examined for homozygous deletion of *SMN1* exon 7. The average relative quantity (aRQ) of *SMN1* exon 7 copies was determined. Newborns whose samples exhibited an aRQ ≥ 0.8 were considered test negative. For samples with an aRQ < 0.8 and samples of insufficient quality, a new dried blood spot was punched out and tested. Final test-positive findings (RQ = 0) were clinically examined, and the screening result as well as the presence of 2 *SMN2* copies confirmed in an external laboratory.

4.4.2 Available assessment-relevant outcomes

For the assessment of suitable diagnostic test methods, 4 studies on diagnostic quality with a VOPT design were analysed (Chien 2017, Czibere/Vill 2019, Kariyawasam 2019, Kraszewski 2018). This study design is suitable for calculating the PPV only. Conclusions on specificity can be drawn only if no false positive events occurred.

4.4.3 Assessment of the risk of bias and transferability

The risk of bias of the Chien 2017, Czibere/Vill 2019, and Kariyawasam 2019 studies on diagnostic quality was rated as low. Likewise, there were only minor concerns about the transferability of results from these studies.

Kraszewski 2018 was rated as having a high risk of bias because there were uncertainties regarding patient selection as well as the index test. For one thing, children of mothers who spoke English or Spanish were included in the study exclusively on weekdays. Therefore, it remains unclear whether the newborns were consecutively included and whether inadequate

study exclusions were avoided. For another, parts of the index test were conducted manually. This manual execution also led to the transferability of the index test being rated as unclear. A summary assessment nevertheless rated the concerns regarding the transferability of results of the Kraszewski 2018 study as minor.

4.4.4 Results on outcomes

The Chien 2017 study used a 2-stage procedure to analyse the dried blood spots: In a 1st step, 15 newborns tested positive in RT-PCR. In a 2nd step, the same sample material of these 15 newborns was examined with subsequent ddPCR. While the latter produced final negative findings for 8 newborns, 7 newborns still had positive test results. This 2-stage method did not result in any false positives; therefore, both PPV and specificity were 100% (PPV 100; 95% CI: [64.6; 100]). The ongoing Czibere/Vill 2019 study, which analyses dried blood spots by means of qPCR, likewise reports no false positive findings at a data cut-off after one and a half years; therefore, both PPV and specificity were 100% (PPV 100; 95% CI: [88.6; 100]). So far, a total of 30 newborns with 5q-linked SMA have been detected in this study. For the Kraszewski 2018 study, in which the analysis was done by means of qPCR as well, no false positive findings were reported. That is, both PPV and specificity were 100% in this study as well (PPV 100; 95% CI: [20.7; 100], with 1 positively tested newborn).

The Kariyawasam 2019 study was based on a narrower definition of the target disease than the other studies because the index test classified only newborns with < 4 *SMN2* copies as test positive. A 2-stage method very similar to the one used in the Chien 2017 study was employed. Ten newborns tested positive both in the 1st step using RT-PCR and in the 2nd step using subsequent ddPCR. One of these children was found to be false positive in the reference test (PPV 90; 95% CI: [59.6; 98.2]).

Calculating a pooled effect is not meaningful due to the different index tests as well as the different definition of the target disease.

It remains unclear how many affected children were missed by the testing. Given the low prevalence, it is safe to assume that the vast majority of negative test results of the index test is correct. All things considered, the results of the studies on diagnostic quality suggest that the examined test methods are suitable for newborn screening for 5q-linked SMA.

4.5 Summary of the available evidence

No **comparative interventional studies of the screening chain** were found.

Data were available for the comparison of **early versus late symptomatic treatment start**. A hint of effect difference depending on treatment start time in symptomatic children was found for the combined outcome of time to death or permanent ventilation and for the outcome of motor milestone achievement. For both outcomes, children benefit more from an early symptomatic treatment start than from a late symptomatic treatment start. For the outcomes of SAEs, severe AEs, and treatment discontinuation due to AEs, there is no hint of different effects

based on treatment start time in symptomatic children with infantile SMA. For other outcomes, either no data or no usable data were available.

Data were available on the comparison of **presymptomatic versus early symptomatic treatment start**. A dramatic difference was found for the outcome of motor milestone achievement, resulting in a hint of greater benefit of a presymptomatic treatment start versus early symptomatic treatment start. For the outcomes of serious adverse events and severe adverse events, statistically significant differences were found in favour of a presymptomatic treatment start. Each of these observed differences are rated as too small to not be explicable solely by the impact of confounding factors. Hence, for each of them, there is no hint of lesser harm of a presymptomatic versus early symptomatic treatment start. For each of the outcomes of overall survival, permanent ventilation, treatment discontinuation due to AEs, and back pain (as an SAE or severe AE), no statistically significant differences were found. The criteria of a dramatic effect were not met. Hence, for each of them, there is no hint of greater or lesser benefit or harm of a presymptomatic versus early symptomatic treatment start. For other outcomes, no usable data were available.

The results of the **studies on diagnostic quality** suggest that the examined test methods are suitable for newborn screening for 5q-linked SMA. No data are available on the number of false negative results.

All things considered, on the basis of the compilation of the available results on treatment start as well as on diagnostic quality by means of the linked evidence approach, there is an indication of a benefit of newborn screening for 5q-linked SMA in comparison with no newborn screening.

5   Classification of the assessment result

Evidence regarding earlier treatment start

Early versus late symptomatic start of nusinersen treatment

Only 1 small RCT with potentially highly biased results was available for the assessment of an early versus late symptomatic treatment start with nusinersen, the only drug so far approved in Germany for children with neonatal disease onset (< 7 months). Hence, the study supplies data on only some of the children with 5q-linked SMA, namely those with infantile onset SMA (also known as SMA type I). In addition, due to premature discontinuation of the study, data are available only for a limited follow-up duration (median: < 10 months); long-term results, e.g. on adverse events, are therefore not available.

The results of the ENDEAR study suggest that in children with infantile-onset 5q-linked SMA, a start of nusinersen treatment within 12 weeks after symptom onset is of benefit when compared with a later treatment start in terms of their risk of death or need for continuous assisted ventilation as well as motor milestone achievement.

Data on (S)AEs were available from the published Module 4 of the dossier [38] for the G-BA's benefit assessment of the drug nusinersen [49] and from supplementary manufacturer documents with regard to the subgroups relevant for the report (early versus late symptomatic treatment start) regarding the outcomes of SAEs, treatment discontinuation due to AEs, and severe AEs. No statistically significant interaction was found for any of the 3 outcomes; consequently, any differences in these outcomes between early and late symptomatic treatment start are presumably not important. Since the (S)AEs which occurred have not been individually described, these results are not fully interpretable. It remains unclear which (S)AEs are more common or less common in children with early versus late symptomatic treatment start. However, the following information can be derived on the basis of the results of the total study population: In the study report, no SAE is classified as being due to the study drug [33]. A few AEs (not classified as serious) were associated with the method of administration (lumbar puncture), e.g. nausea and postprocedural swelling [33, 50]. Serious respiratory events were found in all analysed children of both treatment groups [38], but the analysis and operationalization of this outcome lacked clarity (also see [49]). In terms of the occurrence of severe AEs, a statistically significant difference was found in favour of nusinersen (n = 45 [56%] when compared with the sham procedure n = 33 [80%]; OR: 0.31; 95% CI: [0.13; 0.76]; p < 0.010 [38]). Due to the greater number of deaths in the control group, the duration of follow-up and hence exposure tended to be longer for children in the nusinersen group, which underscores the results in favour of nusinersen treatment. These results illustrate the fact that the observed events cannot be interpreted as exclusively treatment side effects, but can be largely explained by symptoms or progression of the primary disease. Even if harmful effects were to be found for some AEs, it would be safe to assume for this seriously ill patient population, that such harmful effects would not fully outweigh the demonstrated benefits of an earlier treatment start in terms of the combined outcome of time to death or permanent ventilation as well as the outcome of motor milestone achievement. For all of the above items,

one caveat to be noted however, is that the available results are based on a very limited follow-up period which does not cover potential long-term harm, and this aspect thus remains unclear. Consequently, there are no long-term data on the tolerability of the drug and on any potential immune responses which might arise in the long term [51]. Particularly the administration method – repeated intrathecal injections (lumbar puncture) – might lead to (S)AEs in the long term. In the CHERISH study on older toddlers with 5q-linked SMA, the adverse event of post-puncture syndrome, for instance, was associated with the lumbar puncture [38]. Some of these questions might be answered in a few years by the ongoing observational study SHINE [27]. This study collects long-term data on patients treated with nusinersen in the intervention group of the included ENDEAR study or in further studies such as CHERISH [52–55] or EMBRACE [56, 57].

Many other questions remain unanswered as well. For instance, the optimal treatment duration is currently unclear. Further, administration is often difficult in patients with scoliosis [23] or spondylodesis [58] and frequently requires guidance by contrast-enhanced imaging, anaesthesia, and usually inpatient monitoring [59, 60]. Potential effects of the repeated anaesthesia associated with intrathecal administration on toddler brain development are being debated as well [61–63]. Further, the risk of cancer increases if the lumbar puncture is radiologically guided [58, 64, 65].

Presymptomatic versus early symptomatic start of nusinersen treatment

Only 1 small retrospective comparative study, which the manufacturer supplied upon request, was available to examine any benefit of moving up the treatment start time from the symptomatic to the presymptomatic phase. This study comprises exclusively children with 2 *SMN2* copies (due to low case numbers, it was not possible to include data on children with 3 *SMN2* copies in this benefit assessment). Therefore, the study provides information exclusively on the subpopulation of children with the most severe course of 5q-linked SMA, i.e. children already diagnosed with infantile SMA (comparator group with early symptomatic treatment start) or those who would most likely develop infantile SMA if left untreated (intervention group with presymptomatic treatment start). Results were available only for the age of 1 year; hence, no long-term results, e.g. on adverse events, were available.

The results of the Biogen 2019 study suggest that children with diagnosed 5q-linked SMA, 2 *SMN2* copies, and hence a likely prognosis of infantile SMA benefit most from nusinersen therapy if it is started already in the presymptomatic phase. Advantages were found particularly regarding motor milestone achievement and are not explicable solely by bias (dramatic effect).

The results provided by the manufacturer on children with 3 *SMN2* copies are in the same direction as the results of the children with 2 *SMN2* copies [39] and therefore support the demonstrated benefits of a presymptomatic treatment start.

If the comparator group of the Biogen 2019 study had included not only children with an early symptomatic treatment start, but all children with a symptomatic treatment start in the

ENDEAR study, the observed benefits of a presymptomatic treatment start would presumably have been even greater.

Summary analysis of the data on treatment start

All things considered, the treatment-related data included in this benefit assessment reveal a "timing–effect relationship" similar to a "dose–effect relationship" with a positive association between earlier treatment start and better treatment results.

Evidence on diagnostic quality

The 4 included studies on diagnostic quality have a VOPT design; therefore, it remains unclear how many children are missed by diagnostic testing for 5q-linked SMA. In general, however, the results of the studies on diagnostic quality suggest that the examined test methods are suitable for newborn screening for 5q-linked SMA.

Heterozygous carriers can be identified with the examined test methods. Heterozygous carriers do not manifest SMA. Collecting information on carrier status as part of a health screening is problematic according to §16 of the German Genetic Diagnostics Act since, pursuant to the explanatory memorandum to the act, screening for carriers of recessive disorders is unlawful [66]. This must be taken into account in the event that the introduction of newborn screening for SMA is considered in Germany.

Consequences of the results for newborn screening

Patients with a later SMA disease onset

The evidence found to answer this report's research question shows that children with diagnosed 5q-linked SMA and a prognosis or confirmation of the infantile form would benefit from newborn screening. No relevant treatment studies were found on patients with later-onset SMA; therefore, it remains unclear whether newborn screening would benefit them as well. Generally, however, such screenings detect all SMA types (except for those with heterozygous deletion and point mutation on the existing *SMN1* gene, which is the case in about 5% of patients). There are ethical implications regarding the early diagnosis of later-onset SMA (onset not until years later) because the age of onset of SMA with ≥ 4 *SMN2* copies cannot be as reliably predicted as that of infantile SMA [14]. The included diagnostic studies handled these patients in different ways. In Chien 2017, the study team tried not to worry patients with later-onset SMA (or their parents). They were asked to contact the team only if symptoms arose. In its publication, the study team calls for a well-considered approach, weighing the potential benefits and psychological distress of newborn screening for patients with ≥ 4 *SMN2* copies ([14], see also [67]). The authors of the Kraszewski 2018 study address this subpopulation as well [45]. They call for additional data to determine whether patients with ≥ 4 *SMN2* copies should start treatment already as newborns and, if so, how frequently this treatment should be administered. The German newborn screening project (Czibere/Vill 2019 [41, 42]) employed a strategy based on the current recommendations of the U.S. working group of Glascock et al. [68]. This strategy involves observing children with ≥ 4 *SMN2* copies by means of a

conservative treatment strategy (monitoring). Using this method, initial clinical symptoms were recognized in an affected 8-month-old infant, and treatment was immediately initiated. This case confirms that the prediction of the age of SMA onset is less reliable in patients with ≥ 4 *SMN2* copies than in patients with < 4 *SMN2* copies. The method used in the Australian newborn screening programme according to Kariyawasam 2019 [44] would not have identified this infant. This programme defined the target disease more narrowly for the screening test in order to explicitly avoid identifying patients with later-onset SMA. Only infants with < 4 *SMN2* copies were defined as test positive. Individuals with ≥ 4 *SMN2* copies were described as test negative and not reported.

Infants who, in the newborn screening, are found to have ≥ 4 *SMN2* copies might not necessarily have late-onset SMA. It currently remains unclear whether patients who do have late-onset SMA would benefit from newborn screening. The data found on treatment start in children with diagnosed 5q-linked SMA and prognosis or confirmation of the infantile form are not necessarily transferable to patients with late-onset SMA (also see [68]). If newborn screening is introduced, it is essential to consider how to appropriately handle these children and their families – including the option of letting them decide for themselves whether they would like to receive this information.

Key treatment studies without relevance to the report

In addition to the included ENDEAR study, CHERISH is a key study [52–55] in which nusinersen was used to treat patients with late-onset 5q-linked SMA. In this multicentre RCT, 126 symptomatic children were randomly allocated to treatment with nusinersen or a sham injection. Inclusion criteria were, among others, symptom onset at ≥ 6 months of age and study inclusion at between 2 and 12 years of age. The median patient age at study inclusion was 4 years in the nusinersen group and 3 years in the sham treatment group. Initial symptoms were found at a mean age of 10 months in the nusinersen group and 11 months in the sham procedure group. The mean disease duration (age at study inclusion minus age at symptom onset) was 39 months (nusinersen group) and 30 months (sham treatment group). Diagnosis and treatment start were separated by about 30 months (nusinersen group) and 18 months (sham treatment group). This differs from the current healthcare situation in Germany, where, ever since nusinersen was approved, treatment has usually been started immediately after diagnosis. Therefore, the study was excluded as irrelevant. In addition, said study does not contribute any data on newborn screening. It was not suitable for determining at what time children with late-onset SMA who are identified by newborn screening should ideally start therapy – for instance, immediately after birth, at the initial onset of symptoms, or shortly prior to onset, provided that symptom onset can be predicted with sufficient reliability.

The EMBRACE study on the use of nusinersen in patients with 5q-linked SMA should be mentioned as well [56, 57, 69]. It randomly allocated 21 children who were not eligible for inclusion in the ENDEAR study nor in the CHERISH study to receive treatment with nusinersen or a sham injection. The study was recently completed. No full publication is available, but initial results have been reported in the study registry entry [69]. This study was assessed as

irrelevant for the present benefit assessment as well. The question regarding earlier versus later treatment start was not the subject of this study but might have been answered on the basis of subgroup analyses. However, the number of children per treatment group (nusinersen n = 14, sham injection n = 7) was too low to perform subgroup analyses in accordance with the research question of the report (earlier versus later treatment start).

New treatment approaches in development

Beyond the drug nusinersen, which has been approved in Germany since 2017, other treatment approaches on the treatment of SMA are currently still in development (see Chapter 1). Notable are two treatment approaches which are currently in the approval process (PRIME) of the European Medicines Agency (EMA). One is an oral drug (risdiplam), and the other, a gene replacement therapy (AVXS-101) which was approved for children under 2 years of age by the U.S. FDA in May 2019 [20, 21]. Since initial study results on AVXS-101 suggest that, in children with infantile SMA, an earlier-age treatment start might contribute to better motor milestone achievement, the authors emphasize the relevance of newborn screening to enable earlier treatment of children with SMA [70]. At this time, however, it is impossible to say to what extent results on these therapies will be able to contribute to this benefit assessment going forward, because the therapy first requires approval in Germany. In the future, however, comparative interventional studies (of the screening chain) on treatments other than nusinersen might become relevant for determining any benefit of newborn screening for 5q-linked SMA.

Ongoing pilot project on newborn screening for SMA in Germany

In Bavaria, a pilot project on newborn screening for cystinosis and SMA has been ongoing since January 2018 [41–43]. This pilot project is a study which can be considered a 1-arm interventional study of the screening chain. Newborns who are diagnosed with SMA in the screening receive standardized treatment on the basis of the number of *SMN2* copies, either directly with nusinersen (≤ 3 *SMN2* copies) or standardized monitoring, so that treatment can be started soon after symptom onset (≥ 4 *SMN2* copies). Due to the 1-arm design, the study fails to meet the requirements for inclusion as a comparative interventional study of the screening chain. As a prospective diagnostic cohort study, however, it does meet the inclusion criteria for studies on diagnostic quality; therefore, it was used in the assessment of the latter (see Section 4.4).

Regarding the results of this earliest possible treatment of the children so far detected through the screening project, Vill 2019 [42] provided initial preliminary results with a very short follow-up period. Due to the lack of a comparator intervention, they cannot be used to answer the question regarding a presymptomatic versus later treatment start. The same applies to results which were made available as part of the commenting procedure (see [71]). These data offer insights into the patients' individual courses of disease and motor milestone achievement of the children so far identified with 2, 3, or 4 *SMN2* copies. The study team reported its plans to compare the children detected in this newborn screening programme with a population of children who were identified after symptom onset and are documented in the SMArtCARE

registry (see A4.3 of the full report). In the form of a retrospective comparative interventional study of the screening chain, such a comparison might potentially provide more insights for the present benefit assessment, provided that these studies met the inclusion criteria (see Chapter 3 as well as a detailed discussion in Section A2.1 of the full report).

Publication bias

The available information does not suggest publication bias.

6 Conclusion

No comparative interventional studies of the screening chain were available for the comparison of newborn screening for 5q-linked spinal muscular atrophy (SMA) versus no newborn screening. Therefore, interventional studies permitting the comparison of an earlier versus later treatment start as well as studies on diagnostic quality were used and combined by means of the linked evidence approach.

For the **comparison of an early versus late symptomatic treatment start**, 1 small randomized controlled study with a short follow-up period can be used; it examined drug therapy in comparison with a sham procedure in children with infantile 5q-linked SMA. For the combined outcome of time to death or permanent ventilation as well as for the outcome of motor milestone achievement, subgroup analyses revealed effect differences between children with an early symptomatic treatment start (disease duration ≤ 12 weeks) and children with a later treatment start (disease duration > 12 weeks). For both outcomes, children benefit more from an early symptomatic treatment start than from a late symptomatic treatment start. The outcomes of serious adverse events, severe adverse events, and treatment discontinuation due to adverse events each showed no effect differences between subgroups. For other outcomes, no usable data were available.

For the **comparison of a presymptomatic versus an early symptomatic treatment start**, 1 small retrospective comparative study, which was made available by the manufacturer upon request, was included. Data were available on children with diagnosed 5q-linked SMA and 2 *SMN2* copies (i.e. prognosis or confirmation of infantile SMA). For the outcome of motor milestone achievement, large effects were found in favour of a presymptomatic treatment start over early symptomatic treatment start (disease duration ≤ 12 weeks); these effects were not explicable solely by bias (dramatic effect). For the outcomes of serious adverse events and severe adverse events, statistically significant differences were found in favour of a presymptomatic treatment start. These observed differences were assessed as small enough to be explicable solely by the effect of confounders. For each of the outcomes of overall survival, permanent ventilation, treatment discontinuation due to AEs, and back pain, no statistically significant differences were found. The criteria of a dramatic effect were not met. No data were requested on other outcomes.

It was not possible to include any comparative interventional studies on **patients with a later disease onset than in the infantile form**.

For the assessment of **diagnostic quality**, it was possible to include 4 studies, but these studies verified only positive test results (verification-of-only-positive-testers design). The results of these studies suggest that the examined test methods are suitable for newborn screening for 5q-linked SMA. It remains unclear how many affected children were missed by the testing.

In summary, there is an indication of benefit of newborn screening for 5q-linked SMA when compared with no screening. This result is based, first, on data on the presymptomatic, early

symptomatic, and late symptomatic drug treatment of children with diagnosed 5q-linked SMA and a prognosis or confirmation of the infantile form. The included data show an association between timing and effect according to which an earlier treatment start is associated with better treatment results. Second, the derivation of an indication of benefit of newborn screening is based on the suitability of diagnostic test methods and the opportunity to achieve an earlier diagnosis (and hence treatment) by means of newborn screening. The available data do not permit drawing any conclusions as to whether children identified by the screening to have late-onset SMA (i.e. symptom onset not until years later) would benefit from a presymptomatic treatment start. Currently, it is therefore especially unclear how to handle newborns who test positive in the screening and are expected to have late-onset disease (≥ 4 *SMN2* copies). If newborn screening is introduced, it will be essential to consider how to appropriately handle these children and their families – including the option of letting them decide for themselves whether or not they wish to know about the presence of mild courses of SMA forms.

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Please see full final report for full reference list.

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https://www.iqwig.de/en/projects-results/projects/non-drug-interventions/s-projekte/s18-02-newborn-screening-for-spinal-muscular-atrophy-sma.10782.html

Appendix A – Search strategies

A.1 – Searches in bibliographic databases

A.1.1 – Search strategies for comparative intervention studies of the screening chain and studies on diagnostic accuracy

1. MEDLINE

Search interface: Ovid

▪   Ovid MEDLINE(R) ALL 1946 to October 21, 2019

#	Searches
1	exp muscular atrophy, spinal/
2	(spinal* adj1 muscular* adj1 atroph*).ti,ab.
3	or/1-2
4	exp infant/
5	(newborn* or neonat* or pediatric* or infant*).ti,ab.
6	or/4-5
7	neonatal screening/
8	and/3,7
9	*mass screening/
10	screen*.ti,ab.
11	or/9-10
12	and/3,6,11
13	exp smn complex proteins/
14	exp exons/
15	(smn1* or smn2* or (smn* adj1 ("1" or "2"))).ti,ab.
16	(survival* adj3 motor* adj1 neuron*).ti,ab.
17	(exon7* or (exon* adj1 "7")).ti,ab.
18	or/13-17
19	and/3,6,18
20	or/8,12,19
21	20 not (exp animals/ not humans.sh.)
22	21 not (comment or editorial).pt.
23	22 and (english or german).lg.

2. Embase

Search interface: Ovid

- Embase 1974 to 2019 October 21

#	Searches
1	exp spinal muscular atrophy/
2	(spinal* adj1 muscular* adj1 atroph*).ti,ab.
3	or/1-2
4	exp infant/
5	(newborn* or neonat* or pediatric* or infant*).ti,ab.
6	or/4-5
7	newborn screening/
8	and/3,7
9	screen*.ti,ab.
10	and/3,6,9
11	survival motor neuron protein/
12	survival motor neuron protein 1/
13	survival motor neuron protein 2/
14	smn1 gene/
15	smn2 gene/
16	protein smn1/
17	protein smn2/
18	exon/
19	(smn1* or smn2* or (smn* adj1 ("1" or "2"))).ti,ab.
20	(survival* adj3 motor* adj1 neuron*).ti,ab.
21	(exon7* or (exon* adj1 "7")).ti,ab.
22	or/11-21
23	and/3,6,22
24	or/8,10,23
25	24 not medline.cr.
26	25 not (exp animal/ not exp human/)
27	26 not (conference abstract or conference review or editorial).pt.
28	27 and (english or german).lg.

3. The Cochrane Library

Search interface: Wiley

- Cochrane Database of Systematic Reviews: Issue 10 of 12, October 2019

- Cochrane Central Register of Controlled Trials: Issue 10 of 12, October 2019

ID	Search
#1	[mh "muscular atrophy, spinal"]
#2	(spinal* near/1 muscular* near/1 atroph*):ti,ab
#3	#1 or #2
#4	[mh "infant"]
#5	(newborn* or neonat* or pediatric* or infant*):ti,ab
#6	#4 or #5
#7	[mh ^"neonatal screening"]
#8	#3 and #7
#9	[mh ^"mass screening"]
#10	screen*:ti,ab
#11	#9 or #10
#12	#3 and #6 and #11
#13	[mh "smn complex proteins"]
#14	[mh "exons"]
#15	(smn1* or smn2* or (smn* near/1 (1 or 2))):ti,ab
#16	(survival* near/3 motor* near/1 neuron*):ti,ab
#17	(exon7* or (exon* near/1 7)):ti,ab
#18	#13 or #14 or #15 or #16 or #17
#19	#3 and #6 and #18
#20	#8 or #12 or #19 in Cochrane Reviews, Cochrane Protocols
#21	#8 or #12 or #19 in Trials

4. Health Technology Assessment Database

Search interface: Centre for Reviews and Dissemination

Line	Search
1	MeSH DESCRIPTOR Muscular Atrophy, Spinal EXPLODE ALL TREES
2	(spinal* AND muscular* AND atroph*)
3	#1 OR #2
4	MeSH DESCRIPTOR Infant EXPLODE ALL TREES
5	(newborn* OR neonat* OR pediatric* OR infant*)

Line	Search
6	#4 OR #5
7	MeSH DESCRIPTOR Neonatal Screening
8	#3 AND #7
9	MeSH DESCRIPTOR Mass Screening
10	(screen*)
11	#9 OR #10
12	#3 AND #6 AND #11
13	MeSH DESCRIPTOR SMN Complex Proteins EXPLODE ALL TREES
14	MeSH DESCRIPTOR Exons EXPLODE ALL TREES
15	(smn1* OR smn2* OR (smn* NEXT (1 OR 2)))
16	(survival* AND motor* AND neuron*)
17	(exon7* OR (exon* NEXT 7))
18	#13 OR #14 OR #15 OR #16 OR #17
19	#3 AND #6 AND #18
20	#8 OR #12 OR #19
21	(#20) IN HTA

A.1.2 – Search strategies for comparative intervention studies at the start of treatment

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to October Week 2 2019

- Ovid MEDLINE(R) Daily Update October 21, 2019

#	Searches
1	exp muscular atrophy, spinal/
2	(spinal* adj1 muscular* adj1 atroph*).ti,ab.
3	or/1-2
4	exp physical therapy modalities/
5	rehabilitation.fs.
6	(physiotherap* or exercise* or gymnastic* or massage* or mobilization* or stretching*).ti,ab.
7	(therap* adj3 (manual* or physical*)).ti,ab.
8	((muscle* or relaxation* or strength* or endurance* or fitness* or physical* or restistance*) adj1 training*).ti,ab.
9	nusinersen*.mp.

#	Searches
10	or/4-9
11	and/3,10
12	11 not (exp animals/ not humans.sh.)
13	12 not (comment or editorial).pt.
14	13 and (english or german).lg.

Search interface: Ovid

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to October 21, 2019

- Ovid MEDLINE(R) Epub Ahead of Print October 21, 2019

#	Searches
1	(spinal* adj1 muscular* adj1 atroph*).ti,ab.
2	(physiotherap* or exercise* or gymnastic* or massage* or mobilization* or stretching*).ti,ab.
3	(therap* and (manual* or physical*)).ti,ab.
4	((muscle* or relaxation* or strength* or endurance* or fitness* or physical* or restistance*) and training*).ti,ab.
5	nusinersen*.mp.
6	or/2-5
7	and/1,6
8	7 not (comment or editorial).pt.
9	8 and (english or german).lg.

2. Embase

Search interface: Ovid

- Embase 1974 to 2019 October 21

#	Searches
1	spinal muscular atrophy/
2	exp hereditary spinal muscular atrophy/
3	(spinal* adj1 muscular* adj1 atroph*).ti,ab.
4	or/1-3
5	physiotherapy/
6	exp kinesiotherapy/
7	massage/

#	Searches
8	(physiotherap* or exercise* or gymnastic* or massage* or mobilization* or stretching*).ti,ab.
9	(therap* adj3 (manual* or physical*)).ti,ab.
10	((muscle* or relaxation* or strength* or endurance* or fitness* or physical* or restistance*) adj1 training*).ti,ab.
11	nusinersen*.mp.
12	or/5-11
13	and/4,12
14	13 not medline.cr.
15	14 not (exp animal/ not exp human/)
16	15 not (conference abstract or conference review or editorial).pt.
17	16 and (english or german).lg.

3. The Cochrane Library

Search interface: Wiley

- Cochrane Database of Systematic Reviews: Issue 10 of 12, October 2019

- Cochrane Central Register of Controlled Trials: Issue 10 of 12, October 2019

ID	Search
#1	[mh "muscular atrophy, spinal"]
#2	(spinal* near/1 muscular* near/1 atroph*):ti,ab
#3	#1 or #2
#4	[mh "physical therapy modalities"]
#5	[mh /rh]
#6	(physiotherap* or exercise* or gymnastic* or massage* or mobilization* or stretching*):ti,ab
#7	(therap* near/3 (manual* or physical*)):ti,ab
#8	((muscle* or relaxation* or strength* or endurance* or fitness* or physical* or restistance*) near/1 training*):ti,ab
#9	nusinersen*
#10	#4 or #5 or #6 or #7 or #8 or #9
#11	#3 and #10 in Cochrane Reviews, Cochrane Protocols
#12	#3 and #10 in Trials

4. Health Technology Assessment Database

Search interface: Centre for Reviews and Dissemination

Line	Search
1	MeSH DESCRIPTOR Muscular Atrophy, Spinal EXPLODE ALL TREES
2	(spinal* AND muscular* AND atroph*)
3	#1 OR #2
4	MeSH DESCRIPTOR Physical Therapy Modalities EXPLODE ALL TREES
5	(physiotherap* OR exercise* OR gymnastic* OR massage* OR mobilization* OR stretching*)
6	(therap* AND (manual* OR physical*))
7	((muscle* OR relaxation* OR strength* OR endurance* OR fitness* OR physical* OR restistance*) AND training*)
8	(nusinersen*)
9	#4 OR #5 OR #6 OR #7 OR #8
10	#3 AND #9
11	(#10) IN HTA

A.2 – Searches in study registries

ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Advanced Search

Search strategy
spinal muscular atrophy

2. EU Clinical Trials Register

Provider: European Medicines Agency

- URL: https://www.clinicaltrialsregister.eu/ctr-search/search
- Type of search: Basic Search

Search strategy
nusinersen OR isis396443 OR isis-396443 OR (isis 396443)

3. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

▪ URL: http://apps.who.int/trialsearch/

▪ Type of search: Standard Search

Search strategy
spinal muscular atrophy

4. Biogen Clinical Trial Results

Provider: Biogen

▪ URL: http://clinicalresearch.biogen.com/Study/ByProduct/18

Search strategy
Search by Product / SPINRAZA (nusinersen)