NIS PROTOCOL (SECONDARY DATA USE)

TITLE:	**EVALUATION OF A REAL WORLD DATA COLLECTION FOR THE REASSESSMENT OF THE ADDITIONAL BENEFIT OF EVRYSDI® (RISDIPLAM)**
PROTOCOL NUMBER:	ML44661
VERSION NUMBER:	3.0
STUDIED MEDICINAL PRODUCT:	EVRYSDI® (RISDIPLAM)
PRODUCT REFERENCE NUMBER{S}	European Union (EU) marketing authorization number: EU/1/21/1531/001
AUTHOR:	[redacted]
DATE FINAL:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

MARKETING AUTHORIZATION HOLDER{S} (MAH) or STUDY INITIATOR:	Roche Registration GmbH Emil-Barell-Strasse 1 D-79639 Grenzach-Wyhlen Germany
RESEARCH QUESTION AND OBJECTIVES:	The objective of this study is to evaluate the comparative effectiveness and safety of risdiplam versus a therapy according to physician´s choice taking into account nusinersen and onasemnogene abeparvovec. The research questions are a result of the participation process with G-BA, the G-BA appraisal, the G-BA advice and discussions with medical experts regarding the evaluation of a real world data collection for the reassessment of the additional benefit of risdiplam. According to the requirements of the G-BA the study follows a non-randomized design comparing risdiplam with nusinersen and onasemnogene abeparvovec. Safety data is analyzed to allow a comparison of risdiplam versus a therapy according to physician´s choice taking into account nusinersen and onasemnogene abeparvovec.
COUNTRIES OF STUDY POPULATION:	Germany, Austria

TABLE OF CONTENTS

PROTOCOL ACCEPTANCE FORM

-not applicable-

TITLE:	**EVALUATION OF A REAL WORLD DATA COLLECTION FOR THE REASSESSMENT OF THE ADDITIONAL BENEFIT OF EVRYSDI® (RISDIPLAM)**
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MARKETING AUTHORIZATION HOLDER{S} (MAH), or STUDY INITIATOR:	Roche Registration GmbH Emil-Barell-Strasse 1 D-79639 Grenzach-Wyhlen Germany

I agree to conduct the study in accordance with the current protocol.

_____

Treating Physician's Name (print)

_____ _____

Treating Physician's Signature Date

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Events
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	Confidence Interval
CRO	Contract Research Organization
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GPP	Good Pharmacoepidemiological Practice
HFMSE	Hammersmith Functional Motor Scale Expanded
ICH	International Conference on Harmonization
ICSR	Individual Case Safety Report
IRB	Institutional Review Board
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities,
NBS	Newborn Screening
RULM	Revised Upper Limb Module
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SMA	Spinal Muscular Atrophy
SMN 1/2	Survival Motor Neuron 1/2
SmPC	Summary of Product Characteristics
WHO	World Health Organization

2. RESEARCH TEAM

External Scientific Leader

[redacted]

Scientific Responsible

[redacted]

NIS Data Science Responsible

[redacted]

Protocol Development Responsible

[redacted]

Complementary information is given in

3. SYNOPSIS

TITLE:	**EVALUATION OF A REAL WORLD DATA COLLECTION FOR THE REASSESSMENT OF THE ADDITIONAL BENEFIT OF EVRYSDI® (RISDIPLAM)**
PROTOCOL NUMBER:	ML44661
VERSION NUMBER:	3.0
DATE OF SYNOPSIS:	24.06.2024
STUDIED MEDICINAL PRODUCT	EVRYSDI® (RISDIPLAM)
MAIN AUTHOR:	[redacted]
INDICATION:	Spinal Muscular Atrophy (SMA)
MARKETING AUTHORIZATION HOLDER:	Roche Registration GmbH Emil-Barell-Strasse 1 D-79639 Grenzach-Wyhlen Germany
Rationale and background	The objective of this study is to evaluate the comparative effectiveness and safety of risdiplam versus a therapy according to physician´s choice taking into account nusinersen and onasemnogene abeparvovec. The described study design is based on the previous exchange with the Gemeinsamer Bundesausschuss (G-BA, Federal Joint Committee) and scientific experts (1–6). Based on the previous assumptions on the specifics of the disease, the regulatory requirements and the novelty of this project, futility will be checked in the interim analysis.
Research question and objectives	The primary objectives for this study are as follows (presented by population): **Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the survival motor neuron 2 (*SMN2*) gene:**

- To evaluate the safety of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as number of adverse events (AE) leading to hospitalization over time

Symptomatic patients with a clinically diagnosed SMA type 1:

- To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as time to death or permanent ventilation

Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene:

- To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as change from baseline of the Revised Upper Limb Module (RULM) total score at 36 months after treatment start

Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:

- To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as change from baseline of RULM total score at 36 months after treatment start

The secondary objectives for this study are as follows:

- To assess the oral treatment with risdiplam compared to nusinersen or onasemnogene abeparvovec for
  - Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene
  - Symptomatic patients with a clinically diagnosed SMA type 1
  - Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene
  - Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene

including the following variables:

- Mortality
  - Death
- Morbidity
  - Motorfunction (assessed with age-appropriate instruments)
  - Achievement and loss of motor milestones (World Health Organization (WHO) motor development milestones)
  - Respiratory function (need for permanent ventilation)

- Bulbar function (ability to swallow, need for non-oral nutritional support, ability to speak)
- Other complications of disease (e.g. orthopedic complications)

The safety objectives for this study are as follows:

- To assess the safety and tolerability of oral treatment with risdiplam compared to nusinersen or onasemnogene abeparvovec for
  - Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene
  - Symptomatic patients with a clinically diagnosed SMA type 1
  - Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene
  - Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene

including the following safety variables:

- Number of adverse events (AE) leading to hospitalization over time
- Proportion of patients with a serious adverse event (SAE)
- Proportion of patients with an adverse event (AE) leading to hospitalization
- Proportion of patients with a selected SAE: retinopathy, effect on epithelial tissue, thrombocytopenia, nephropathy, hydrocephalus, hepatopathy, cardiac events, sensory neuropathy

Study design

Registry-based study, comparative, non-interventional, multicentric, multinational, open-label. As the treatment start date differs there will be simultaneously enrolled controls and not simultaneously enrolled controls.

Start Date of Study:
The planned start of this study is after confirmation of the submitted study protocol and statistical analysis plan by the G-BA.

Start of treatment with risdiplam is March 26, 2021 at the earliest. Start of treatment with nusinersen is May 30, 2017 at the earliest. Start of treatment with onasemnogene abeparvovec is May 18, 2020 at the earliest.

End of Study

All patients in the study should generally be followed up for at least 36 months. Follow-up time can vary between patients depending on their entry date in the registry.

The planned end of study date is January 01, 2026. Data that is documented in the study database after that time point will not be taken into account.

Length of Study

Interim analysis are planned 12 and 24 months after start of the study and will be handed in to G-BA latest 18 and 30 months after the start of the study. Final analysis will take place in January 2026.

Data sources

This registry-based study is based on the data of the SMArtCARE registry. The SMArtCARE project (www.smartcare.de) provides a platform to collect longitudinal clinical routine data on SMA patients in Germany, Austria and Switzerland. Data from Germany and Austria will be used for this analysis.

Patients' data will be recorded on case report forms (CRFs). The degree of detail and completeness of data collected is dependent on local clinical practice. Data from patient notes should be entered on the CRF as soon as they become available.

An electronic data capture (EDC) system will be used in this registry. Each patient will be identified in the registry by a unique patient identification code (patient number) that is assigned when the patient is registered and is retained as the primary identifier for the patient throughout entire participation in the registry and also in case the patient returns to registry participation after a temporary discontinuation.

Population

Patients must meet the following criteria for study entry:

For all populations:

- Signed informed consent form (if applicable by legal representative) to participate in the study
- Genetically confirmed 5q-autosomal recessive SMA
- Treatment according to the Summary of Product Characteristics (SmPC) with risdiplam OR nusinersen OR onasemnogene abeparvovec with treatment starting not earlier than March 26, 2021 for risdiplam, not earlier than May 30, 2017 for nusinersen and not earlier than May 18, 2020 for onasemnogene abeparvovec

Specific to the indicated populations:

Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene:

- Pre-symptomatic diagnosis

- *SMN2* copy number is ≤ 3

Symptomatic patients with a clinically diagnosed SMA type 1:

- Not pre-symptomatic at time of diagnosis
- Onset of symptoms < 6 months OR never achieved ability to sit unaided

Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene:

- Not pre-symptomatic at time of diagnosis
- *SMN2* copy number is ≤ 3
- Onset of symptoms > 6 months and < 18 months OR never achieved ability to walk unaided

Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:

- Not pre-symptomatic at time of diagnosis
- *SMN2* copy number is ≤ 3
- Onset of symptoms > 18 months
- Patient is able to walk unaided OR was able to walk unaided but has lost that ability

Patients who meet any of the following criteria will be excluded from study entry:

- Prior treatment with disease-modifying therapy before the patient was included in the registry (risdiplam, nusinersen OR onasemnogene abeparvovec). Exception: Patients with initial treatment (nusinersen OR risiplam) for less than three months followed by an alternative treatment will not be excluded but assigned to the subsequent treatment (7).
- Current treatment with therapies which effectiveness is being tested for the treatment of SMA: e.g. salbutamol, riluzole, phenylbutyrate, valproate, hydroxyurea
- Current or previous participation in clinical trials

Variables

Primary Variables

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Number of AE leading to hospitalization over time	Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day)	Change from baseline of RULM total score at 36 months after treatment start	Change from baseline of RULM total score at 36 months after treatment start

Secondary Variables

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Overall Survival and event free survival			
Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to death Time to permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to any respiratory support	Time to death Time to permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to any respiratory support	Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to death Time to permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to any respiratory support	Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to death Time to permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to any respiratory support
Achievement of WHO motor development milestones			
Time from first treatment to reaching the WHO motor development milestone of sitting without support Time from first treatment to reaching the WHO motor development milestone of	Time from first treatment to reaching the WHO motor development milestone of sitting without support Time from first treatment to reaching the WHO motor	Time from first treatment to reaching the WHO motor development milestone of walking without support	-

standing without support Time from first treatment to reaching the WHO motor development milestone of walking without support	development milestone of standing without support Time from first treatment to reaching the WHO motor development milestone of walking without support		
Sustainability of motor milestones			
Time from gaining WHO motor development milestone to permanent loss of milestone ability: - Loss of the ability to sit without support - Loss of the ability to stand without support - Loss of the ability to walk without support	Time from gaining WHO motor development milestone to permanent loss of milestone ability: - Loss of the ability to sit without support - Loss of the ability to stand without support - Loss of the ability to walk without support	Time from gaining WHO motor development milestone to permanent loss of milestone ability: - Loss of the ability to walk without support	Time from gaining WHO motor development milestone to permanent loss of milestone ability: - Loss of the ability to walk without support
Motorfunction Tests			
Change from baseline in CHOP-INTEND total score at 12, 24 and 36 months after treatment start*	Change from baseline in CHOP-INTEND total score at 12, 24 and 36 months after treatment start*	Change from baseline in HFMSE total score at 12, 24, 36 months after treatment start** Change from baseline in RULM total score at 12 and 24 months after treatment start***	Change from baseline HFMSE total score 12, 24, 36 months after treatment start** Change from baseline in RULM total score at 12 and 24 months after treatment start***
Walking performance endpoints			
		-	**For ambulatory patients:** Relative change from baseline in walking distance at 12, 24 and 36

			months after treatment start[#] Evaluation of the total walking distance at month 36 after treatment start[#]
Bulbary function			
Proportion of patients with age-appropriate Bayley III scores in the subscales “Expressive Language” and “Receptive Language” at 24 months of age Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after treatment start Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after treatment start	Proportion of patients with age-appropriate Bayley III scores in the subscales “Expressive Language” and “Receptive Language” at 24 months of age Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after treatment start Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after treatment start	Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after treatment start Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after treatment start	Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after treatment start Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after treatment start
Orthopedic complications			
Time to first documentation of scoliosis or orthopedic surgery Time to first documentation of scoliosis Time to first documentation of orthopedic surgery	Time to first documentation of scoliosis or orthopedic surgery Time to first documentation of scoliosis Time to first documentation of orthopedic surgery	Time to first documentation of scoliosis or orthopedic surgery Time to first documentation of scoliosis Time to first documentation of orthopedic surgery	Time to first documentation of scoliosis or orthopedic surgery Time to first documentation of scoliosis Time to first documentation of orthopedic surgery
Hospitalizations			
Number of planned hospitalizations over time	Number of planned hospitalizations over time	Number of planned hospitalizations over time	Number of planned hospitalizations over time

(including hospitalizations for SMA treatment administration	(including hospitalizations for SMA treatment administration)	(including hospitalizations for SMA treatment administration)	(including hospitalizations for SMA treatment administration)

CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, HFMSE = Hammersmith Functional Motor Scale Expanded, *As part of the regular SMArtCARE guidelines the CHOP-INTEND is used for follow-up monitoring of the following patients: Children: All children < 2 years of age; All patients > 2 years of age without ability to sit. Adults: For patients without ability to sit, **As part of the regular SMArtCARE guidelines the HFMSE I used for follow-up monitoring of the following patients: Children > 2 years for all patients with ability to sit; If CHOP INTEND score >50: CHOP INTEND and HFMSE; If CHOP INTEND score >60: HFMSE instead of CHOP INTEND. Adults: All patients with ability to sit, *** As part of the regular SMArtCARE guidelines for follow-up monitoring the RULM is used for follow-up monitoring of the following patients: Children > 2 years and adults: For all patients with ability to sit in a wheelchair (see SMArtCARE: Recommendations for the evaluation of adult patients with SMA), [#]As part of the regular SMArtCARE guidelines for follow-up monitoring used for the following patients: > 2 years for all patients with ability to walk

Safety Variables

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Proportion of patients with a SAE Proportion of patients with an AE leading to hospitalization Proportion of patients with a selected SAE: retinopathy, effect on epithelial tissue, thrombocytopenia, nephropathy, hydrocephalus, hepatopathy, cardiac events, sensory neuropathy	Number of AE leading to hospitalization over time Proportion of patients with a SAE Proportion of patients with an AE leading to hospitalization Proportion of patients with a selected SAE: retinopathy, effect on epithelial tissue, thrombocytopenia, nephropathy, hydrocephalus, hepatopathy, cardiac events, sensory neuropathy	Number of AE leading to hospitalization over time Proportion of patients with a SAE Proportion of patients with an AE leading to hospitalization Proportion of patients with a selected SAE: retinopathy, effect on epithelial tissue, thrombocytopenia, nephropathy, hydrocephalus, hepatopathy, cardiac events, sensory neuropathy	Number of AE leading to hospitalization over time Proportion of patients with a SAE Proportion of patients with an AE leading to hospitalization Proportion of patients with a selected SAE: retinopathy, effect on epithelial tissue, thrombocytopenia, nephropathy, hydrocephalus, hepatopathy, cardiac events, sensory neuropathy

Study size	In this study patients will be enrolled across the German and Austrian SMArtCARE centers (according to the SMArtCARE homepage, there are currently 49 centers in Germany and 13 centers in Austria). The described study design is based on the previous exchange with the G-BA and scientific experts (ref.). Due to insufficient data on effect sizes and the distribution between patients receiving nusinersen and patients receiving onasemnogene abeparvovec, it is not possible to calculate the sample size yet. As stated in the G-BA decision the sample size calculations will be re-assessed at the first interim analysis based on the observed effects and recruiting rates (section 8.7.5) and considering all relevant endpoints. In addition futility will be checked in the interim analysis.
Data Analysis	All analyses are based on the full analysis set (FAS), including all enrolled patients. The participants will be included in the analyses according to the treatment they received at enrollment. To adjust for differences in the confounder variables between the treatment groups, propensity score weighting will be applied if sufficient overlap and balance between the scores is given. Depending on the amount of missing data for the confounder variables, a complete case analysis or multiple imputation prior to propensity score calculation are considered according to the rules defined in the statistical analysis plan (SAP). All primary estimands as defined in Section 8.3 will be evaluated following the treatment-policy strategy to handle intercurrent events (e.g. early discontinuation from the study treatment or treatment switch). Additionally, supplementary estimands with the hypothetical strategy will be investigated as well, as described in the SAP. For hypothesis testing, statistical significance is controlled at the 1-sided, 0.025 alpha level and the shifted null hypothesis. Point estimators will be presented with 2-sided 95% confidence intervals.
Milestones	**First Data Extraction:** The first data extraction is the date from which the variables used for the analysis as per protocol start to be extracted. For details, see section 5. MILESTONES **Last Data Extraction:** The last data extraction is the date from which the minimum set of data required to perform the statistical analyses leading to the results for the primary objective(s) is

completely available. The planned last data extraction date is January 2026.

4. AMENDMENTS AND UPDATES

1. Amendment due to G-BA requirements from April 4th, 2024 (8)

5. MILESTONES

Milestone	Planned Date
First Data Extraction	At study start
Last Data Extraction	January 2026
Status report	6, 18 and 30 months after study start
Interim report	18 and 30 months after study start
Final report of study results (CSR)	Not applicable
Publication submission	August 2026

6. RATIONALE AND BACKGROUND

Spinal muscular atrophy (SMA) is a rare autosomal recessive neuromuscular disorder characterized by the progressive loss of proximal motor neurons leading to muscle weakness and profound neuromotor disability. It is primarily characterized by degeneration of the anterior horn cells of the spinal cord resulting in muscle atrophy and proximal muscle weakness. It is caused by a homozygous deletion in the survival motor neuron 1 (*SMN1*) gene on chromosome 5q13. The severity of the disease is highly variable and correlates with the age of onset and *SMN2* copy number. For classification purposes, patients are usually categorized into three main subtypes based on clinical criteria, including achieving (or failing to achieve) physical motor milestones, age of onset, and expected life span:

- Type 1 SMA (severe infantile type with onset before 6 months of age; infants never sit without support, with death due to respiratory distress usually within 2 years),
- Type 2 SMA (intermediate chronic infantile type with onset after the age of 6 months, children unable to stand or walk without support),
- Type 3 SMA (chronic juvenile type with onset around the age of 18 months, children able to walk until the disease progresses)

For the best possible development or preservation of motor function, it is particularly important that treatment is started as early as possible. In October 2021, the newborn screening (NBS) for SMA was therefore implemented in Germany. This will allow newborns with SMA to be diagnosed immediately after birth. One consequence of the introduction of the NBS for SMA is that fewer symptomatic patients will be diagnosed in the long term.

In all types of SMA, as the disease progresses, clinical symptoms include hypotonia, symmetrical muscle weakness and atrophy (predominantly of the proximal muscles of the shoulder and pelvic girdle), diminished or absent deep tendon reflexes, tremor of fingers and hands, fasciculation of the tongue muscles, and hyporeflexia with orthopedic deformities (contractures, scoliosis). Progressive respiratory failure and frequent pulmonary infections and superinfections are common in Types 1 and 2 SMA. Other common comorbidities include failure to thrive, pneumonia, osteopenia and osteoporosis with pathological fractures, poor cough and secretion clearance, reduced vital capacity, gastroesophageal dysmotility, urinary incontinence, hip dislocation, and joint and muscle pain.

6.1 STUDY RATIONALE

On the basis of the ongoing or completed studies on risdiplam considered for approval, the) identified evidence gaps, particularly comparative data of a treatment with risdiplam versus existing appropriate therapy alternatives are missing for patients.

Thus, the G-BA initiated a procedure to require an evaluation of a real world data collection for the reassessment of the additional benefit of risdiplam with the following PICO scheme requirements.

Population:

- Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene
- Symptomatic patients with a clinically diagnosed SMA type 1
- Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene
- Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene

Intervention:

- Risdiplam

Treatment according to the Summary of Product Characteristics (SmPC).

Comparator:

- Therapy according to physician’s choice taking into account nusinersen und onasemnogene abeparvovec.

Treatment according to the respective SmPC.

Outcome

- Mortality: Number of deaths

- Morbidity:

  Motorfunction (assessed with age-appropriate instruments)

  Achieving and loss of motor milestones (World Health Organization (WHO) motor development milestones)

  Respiratory function (need for permanent ventilation)

  Bulbar function (ability to swallow, need for non-oral nutritional support, ability to speak)

  Other complications of the disease (e.g. orthopedic complications)
- Number of AE leading to hospitalization over time
- Adverse events:

  Proportion of patients with a SAE

  Proportion of patients with an AE leading to hospitalization

  Proportion of patients with a selected SAE: retinopathy, effect on epithelial tissue, thrombocytopenia, nephropathy, hydrocephalus, hepatopathy, cardiac events, sensory neuropathy

7. RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to evaluate the comparative effectiveness and safety of risdiplam versus a therapy according to physician´s choice taking into account nusinersen and onasemnogene abeparvovec. The research questions are a result of the participation process with G-BA, the G-BA appraisal, the G-BA advice and discussions with medical experts regarding the evaluation of a real world data collection for the reassessment of the additional benefit of risdiplam. The research questions will be addressed using registry data from the SMArtCARE registry.

Primary Objectives

The primary objectives for this study are as follows:

- **Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene:**

  To evaluate the safety of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as number of AE leading to hospitalization over time

- **Symptomatic patients with a clinically diagnosed SMA type 1:**

  To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as time to death or permanent ventilation

- **Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene:**

  To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as change from baseline of Revised Upper Limb Module (RULM) total score at 36 months after treatment start

- **Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:**

  To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as change from baseline of RULM total score at 36 months after treatment start

Secondary objectives

The secondary objectives for this study are as follows:

- **Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene:**

  To assess the impact of treatment on time to death or permanent ventilation

  To assess the impact of treatment on time to death

  To assess the impact of treatment on time to permanent ventilation

  To assess the time to any respiratory support

To evaluate the time from first treatment to reaching the WHO motor development milestone of sitting without support

To evaluate the time from first treatment to reaching the WHO motor development milestone of standing without support

To evaluate the time from first treatment to reaching the WHO motor development milestone of walking without support

To evaluate the time from gaining WHO motor development milestone to permanent loss of milestone ability:

- Loss of the ability to sit without support

- Loss of the ability to stand without support

- Loss of the ability to walk without supportTo assess the change from baseline in CHOP-INTEND total score at 12, 24 and 36 months after treatment start

To evaluate the proportion of patients with age-appropriate Bayley III scores in the subscales “Expressive Language” and “Receptive Language” at 24 months of age

To evaluate the proportion of patients with deterioration of swallowing function at 12, 24 and 36 months after treatment start

To evaluate the proportion of patients with need of non-oral nutritional support at 12, 24 and 36 months after treatment start

To assess orthopedic complications by measuring the time to first documentation of scoliosis or orthopedic surgery

To assess orthopedic complications by measuring the time to first documentation of scoliosis

To assess orthopedic complications by measuring the time to first documentation of orthopedic surgery

To assess the number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)

- **Symptomatic patients with a clinically diagnosed SMA type 1:**

To assess the impact of treatment on time to death

To assess the impact of treatment on time to permanent ventilation

To assess the time to any respiratory support

To evaluate the time from first treatment to reaching the WHO motor development milestone of sitting without support

To evaluate the time from first treatment to reaching the WHO motor development milestone of standing without support

To evaluate the time from first treatment to reaching the WHO motor development milestone of walking without support

To evaluate the time from gaining WHO motor development milestone to permanent loss of milestone ability:

- Loss of the ability to sit without support
- Loss of the ability to stand without support
- Loss of the ability to walk without support

To assess the change from baseline in CHOP-INTEND total score at 12, 24 and 36 months after treatment start

To evaluate the proportion of patients with age-appropriate Bayley III scores in the subscales “Expressive Language” and “Receptive Language” at 24 months months of age

To evaluate the proportion of patients with deterioration of swallowing function at 12, 24 and 36 months after treatment start

To evaluate the proportion of patients with need of non-oral nutritional support at 12, 24 and 36 months after treatment start

To assess orthopedic complications by measuring the time to first documentation of scoliosis or orthopedic surgery

To assess orthopedic complications by measuring the time to first documentation of scoliosis

To assess orthopedic complications by measuring the time to first documentation of orthopedic surgery

To assess the number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)

- **Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene:**

To assess the impact of treatment on time to death or permanent ventilation

To assess the impact of treatment on time to death

To assess the impact of treatment on time to permanent ventilation

To assess the time to any respiratory support

To assess the time from first treatment to reaching the WHO motor development milestone of walking without support

To assess the time from gaining WHO motor development milestone to permanent loss of milestone ability:

- Loss of the ability to walk without support

To assess the change from baseline in HFMSE total score at 12, 24, 36 months after treatment start cTo assess the change from baseline in RULM total score at 12 and 24 months after treatment start c

To evaluate the proportion of patients with deterioration of swallowing function at 12, 24 and 36 months after treatment start

To evaluate the proportion of patients with need of non-oral nutritional support at 12, 24 and 36 months after treatment start

To assess orthopedic complications by measuring the time to first documentation of scoliosis or orthopedic surgery

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- **Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:**

To assess the impact of treatment on time to death or permanent ventilation

To assess the impact of treatment on time to death

To assess the impact of treatment on time to permanent ventilation

To assess the time to any respiratory support

To assess the time from gaining WHO motor development milestone to permanent loss of milestone ability:

- Loss of the ability to walk without support

To assess the change from baseline HFMSE total score 12, 24, 36 months after treatment start c

To assess the change from baseline in RULM total score at 12 and 24 months after treatment start

For ambulatory patients: to assess the relative change from baseline in walking distance at 12, 24 and 36 months after treatment start (As part of the regular SMArtCARE guidelines for follow-up monitoring used for the following patients: > 2 years for all patients with ability to walk)

For ambulatory patients: to evaluate the total walking distance at month 36 (As part of the regular SMArtCARE guidelines for follow-up monitoring used for the following patients: > 2 years for all patients with ability to walk)

To evaluate the proportion of patients with deterioration of swallowing function at 12, 24 and 36 months after treatment start

To evaluate the proportion of patients with need of non-oral nutritional support at 12, 24 and 36 months after treatment start

To assess orthopedic complications by measuring the time to first documentation of scoliosis or orthopedic surgery

To assess orthopedic complications by measuring the time to first documentation of scoliosis

To assess orthopedic complications by measuring the time to first documentation of orthopedic surgery

To assess the number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)

Safety Objectives

The safety objectives of this study are as follows:

- **To assess the safety and tolerability of oral treatment with risdiplam compared to nusinersen or onasemnogene abeparvovec:**
  including the following safety variables:

  Number of AE leading to hospitalization over time

  Proportion of patients with SAE

  Proportion of patients with AE leading to hospitalization

  Proportion of patients with selected SAE: retinopathy, effect on epithelial tissue, thrombocytopenia, nephropathy, hydrocephalus, hepatopathy, cardiac events, sensory neuropathy

8. RESEARCH METHODS

8.1 STUDY DESIGN

This study is a registry-based, comparative, non-interventional, multicentric, multinational, open-label study. As the treatment start date differs, there will be simultaneously enrolled controls and not simultaneously enrolled controls.This registry-based study is based on the data of the SMArtCARE registry. The SMArtCARE project (www.smartcare.de) provides a platform to collect longitudinal clinical routine data on SMA patients in Germany, Austria, and Switzerland.

The registry collects data from SMA patients since 2017. Retrospective data for patients treated with nusinersen will be analyzed since the beginning of the registry (May 30, 2017 at the earliest), data for patients treated with onasemnogene abeparvovec since approval in 2020 (May 18, 2020 at the earliest) and data for patients treated with risdiplam since approval in 2021 (March 26, 2021 at the earliest). Details of the registry are given in the SMArtCARE protocol.

Start Date of Study:
The planned start is after confirmation of the submitted study protocol and statistical analysis plan by the G-BA.

Interim Analysis
Interim analysis are planned 12 and 24 months after start of the study and will be handed in to G-BA latest after 18 and 30 months after the start of the study. Based on these interim analysis, a final sample size estimate will be made using more precise effect assumptions. Final analysis will take place in January 2026.

End of Study:
All patients in the study should generally be followed up for at least 36 months. Follow-up time can vary between patients depending on their entry date in the registry.

The planned end date is January 01, 2026. Data that is documented in the study database after that time point will not be taken into account.

8.1.1 Rationale for Study Design

According to the requirements of the G-BA the study follows a non-randomized design comparing risdiplam with nursinersen and onasemnogene abeparvovec. Since the treatment start date differs there will be simultaneously enrolled controls and not simultaneously enrolled controls. The described study design is based on the previous exchange with the G-BA and scientific experts experts (4, 6, 5, 2, 1, 3). Due to insufficient data on effect sizes and the distribution between patients receiving nusinersen and patients receiving onasemnogene abeparvovec, it is not possible to calculate the sample size yet. As stated in the G-BA Beschluss the sample size calculations will be re-assessed at the first interim analysis based on the observed effects and recruiting rates (Section 8.7.5) and considering all relevant endpoints. In addition, futility will be checked in the interim analysis (4).

8.1.2 Number of Patients Observed in the Study

In this study patients will be enrolled across the German and Austrian SMArtCARE centers.

The planned number of cases can’t be determined yet due to insufficient data on effect sizes and the distribution of patients (see section 8.5). Based on the interim analysis, a sample size estimate will be made for each population using the observed effect assumptions.

-

8.1.3 Sites

The registry collects data of patients from Germany and Austria (according to the SMArtCARE homepage, https://www.smartcare.de/).

8.2 SETTING

8.2.1 Selection Criteria

The following criteria regarding data quality as required by G-BA must be fulfilled (especially for historic data):

- Data collection according to SMArtCARE registry protocol
- Exact definition or operationalization of exposures (type and duration of exposures), drug therapy and other accompanying therapies), clinical events, endpoints and confounders
- Use of standard classifications and terminologies
- Use of validated standard survey instruments (questionnaire, scales, tests)
- Study sites trained on data collection and collection
- Implementation of an agreed disease-specific core data set
- Use of exact dates about the patient, the illness, important examinations and treatments/interventions
- Clearly defined inclusion and exclusion criteria for registry patients
- Strategies to avoid unwanted selection during patient inclusion to achieve representativeness
- Requirements to ensure the data completeness for all time points and of the data per time point
- Source data verification for 100% of patients per study site for the primary endpoint and for at least 10% of randomly selected patients of each study site for all other endpoints since the beginning of the data collection
- Ensuring scientific independence and transparency of the register

Patients must meet the following criteria for study entry:

For all populations:

- Signed informed consent form (by legal representative) to participate in the study
- Genetically confirmed 5q-autosomal recessive SMA
- Treatment according to the SmPC with risdiplam OR nusinersen OR onasemnogene abeparvovec with treatment starting no earlier than March 26, 2021 for risdiplam, not earlier than May 30, 2017 for nusinersen and not earlier than May 18, 2020 for onasemnogene abeparvovec.
-

Specific to the indicated populations:

- **Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene:**

  Pre-symptomatic at time of diagnosis

  SMN2 copy number is $\leqslant$ 3

- **Symptomatic patients with a clinically diagnosed SMA type 1:**

  Not pre-symptomatic at time of diagnosis

  Onset of symptoms < 6 months OR never achieved ability to sit unaided

- **Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene:**

  Not pre-symptomatic at time of diagnosis

  SMN2 copy number is $\leqslant$ 3

  Onset of symptoms > 6 months and < 18 months OR never achieved ability to walk unaided

- **Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:**

  Not pre-symptomatic at time of diagnosis

  SMN2 copy number is $\leqslant$ 3

  Onset of symptoms > 18 months

  Patient is able to walk unaided OR was able to walk unaided but has lost that ability

Patients who meet any of the following criteria will be excluded from the evaluation of the real world data collection for the reassessment of the additional benefit of Evrysdi®:

- Prior treatment with disease-modifying therapy before the patient was included in the registry (risdiplam, nusinersen, or onasemnogene abeparvovec). Exception: Patients with initial treatment (nusinersen OR risiplam) for less than three months followed by an alternative treatment will not be excluded but assigned to the subsequent treatment (7).
- Current treatment with therapies whose effectiveness is being tested for the treatment of SMA: e.g. salbutamol, riluzole, phenylbutyrate, valproate, hydroxyurea
- Current or previous participation in clinical trials

8.2.2 Treatment

8.2.2.1 Dosage, Administration, and Compliance

Dosing and treatment duration of any studied medicinal products are according to the respective SmPC.

Risdiplam

The recommended once daily dose of risdiplam is determined by age and body weight (see Table 1). Risdiplam is taken orally once a day after a meal at approximately the same time each day.

Table 1: Dosing regimen by age and body weight

Age* and body weight	Recommended daily dose
< 2 months of age	0.15 mg/kg
2 months to < 2 years of age	0.20 mg/kg
≥ 2 years of age (< 20 kg)	0.25 mg/kg
≥ 2 years of age (≥ 20 kg)	5 mg

*based on corrected age for preterm infants

Risdiplam is taken orally once a day after a meal at approximately the same time each day, using the reusable oral syringe provided. In infants who are breastfed, risdiplam should be administered after breastfeeding. Risdiplam should not be mixed with milk or formula milk. Risdiplam should be taken immediately after it is drawn up into the oral syringe. If it is not taken within 5 minutes, it should be discarded from the oral syringe and a new dose be prepared. If risdiplam spills or gets on the skin, the area should be washed with soap and water. The patient should drink water after taking risdiplam to ensure the medicinal product has been completely swallowed. If the patient is unable to swallow and has a nasogastric or gastrostomy tube in situ, risdiplam can be administered via the tube. The tube should be flushed with water after delivering risdiplam.

Nusinersen

The recommended dosage of nusinersen is 12 mg (5 ml) per administration. Nusinersen treatment should be initiated as early as possible after diagnosis with 4 loading doses on Days 0, 14, 28 and 63. A maintenance dose should be administered once every 4 months thereafter.

Nusinersen is for intrathecal use by lumbar puncture. Treatment should be administered by health care professionals experienced in performing lumbar punctures. Nusinersen is administered as an intrathecal bolus injection over 1 to 3 minutes, using a spinal anesthesia needle. The injection must not be administered in areas of the skin where there are signs of infection or inflammation. It is recommended that the volume of cerebral spinal fluid, equivalent to the volume of nusinersen to be injected, is removed prior to administration of nusinersen. Sedation may be required to administer nusinersen, as indicated by the clinical condition of the patient. Ultrasound (or other imaging techniques) may be considered to guide intrathecal administration of nusinersen, particularly in younger patients and in patients with scoliosis.

Onasemnogene abeparvovec

Onasemnogene abeparvovec is administered as a single-dose intravenous infusion. Patients will receive a dose of nominal 1.1 x 10^{14} vg/kg onasemnogene abeparvovec. The total volume is determined by patient body weight.

Onasemnogene abeparvovec should be administered with a syringe pump as a single intravenous infusion with a slow infusion of approximately 60 minutes. It must not be administered as an intravenous push or bolus. Insertion of a secondary ('back-up') catheter is recommended in case of blockage in the primary catheter. Following completion of infusion, the line should be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection. Starting 24 hours prior to infusion of onasemnogene abeparvovec it is recommended to initiate an immunomodulatory regimen. Prior to initiation of the immunomodulatory regimen and prior to administration of onasemnogene abeparvovec, the patient must be checked for symptoms of active infectious disease of any nature.

8.2.3 Concomitant Medication and Treatment

Concomitant medication will be allowed except for treatments defined as exclusion criterion.

Medication taken on a regular basis is documented in the SMArtCARE database.

8.3 ENDPOINTS AND ESTIMANDS

8.3.1 Primary Objectives and Corresponding Estimands

Table 2: Primary Objectives and Corresponding Estimands

Primary Objective	Estimand Definition
To evaluate the safety of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as the number of AE leading to hospitalization over time	Population: Presymptomatic patients with a 5q-associated SMA and up to three copies of the SMN2 gene as defined by the study inclusion and exclusion criteria (see Section 8.2.1 of the protocol) Endpoint: number of AE leading to hospitalization over time Treatment (see Section 8.2.2 of the protocol):Experimental arm: Risdiplam according to SmPC Control arm: Nusinersen or onasemnogene abeparvovec according to SmPC Intercurrent events and handling strategies: Early discontinuation from study treatment: Treatment-policy strategy Treatment switch: Treatment-policy strategy Population-level summary: Rate ratio
To evaluate the efficacy of risdiplam compared to nusinersen or	Population: Symptomatic patients with a clinically diagnosed SMA type 1 (see Section 8.2.1of the protocol)

Primary Objective	Estimand Definition
onasemnogene abeparvovec measured as time to death or permanent ventilation	Endpoint: Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Treatment: as defined above Intercurrent events and handling strategies: Early discontinuation from study treatment: Treatment-policy strategy Treatment switch: Treatment-policy strategy Population-level summary: hazard ratio
To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as change from baseline of RULM total score	Population: Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene (see Section 8.2.1 of the protocol). Only patients with a baseline value and a value at month 36 after treatment start are included. Endpoint: Change from baseline of RULM total score at 36 months after treatment start Treatment: as defined above Intercurrent events and handling strategies: Early discontinuation from study treatment: Treatment-policy strategy Treatment switch: Treatment-policy strategy Population-level summary: Cohen's d
To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as change from baseline of RULM total score	Population: Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the SMN2 gene (see Section 6.1 of the protocol). Only patients with a baseline value and a value at month 36 after treatment start are included. Endpoint: as defined above Treatment: as defined above Intercurrent events and handling strategies: as defined above Population-level summary: as defined above

Additional information to primary objectives:

Table 3: Operationalization of primary endpoints in SMArtCARE eCRF

Primary Endpoint	Fields of SMArtCARE eCRF
Pre-symptomatic patients Number of AE leading to hospitalization over time	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Adverse events: Date recorded • Adverse events: Has there been any adverse event since the last visit? • Adverse events: Has there been unplanned or prolonged hospitalisation?

	• Adverse events: Start date
Patients with SMA Type 1 Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day)	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • End of data collection: Date of death • Medical assessment: Visit date • Medical assessment: Start of ventilator use • Medical assessment: Ongoing use of ventilator? • Medical assessment: End of ventilator use • Medical assessment: Time of ventilator use = Continuous (>16h/day)
Patients with SMA Type 2 Change from baseline of RULM total score at 36 months after treatment start	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • RULM: Date of assessment • RULM: Total RULM score
Patients with SMA Type 3 Change from baseline of RULM total score at 36 months after treatment start	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • RULM: Date of assessment • RULM: Total RULM score

8.3.2 Secondary Variables

Table 4: Secondary Variables

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Overall Survival and event free survival			
Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to death Time to permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to any respiratory support	Time to death Time to permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to any respiratory support	Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to death Time to permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to any respiratory support	Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to death Time to permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to any respiratory support
Achievement of WHO motor development milestones			
Time from first treatment to reaching the WHO			-

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Overall Survival and event free survival			
motor development milestone of sitting without support Time from first treatment to reaching the WHO motor development milestone of standing without support Time from first treatment to reaching the WHO motor development milestone of walking without support	Time from first treatment to reaching the WHO motor development milestone of sitting without support Time from first treatment to reaching the WHO motor development milestone of standing without support Time from first treatment to reaching the WHO motor development milestone of walking without support	Time from first treatment to reaching the WHO motor development milestone of walking without support	
Sustainability of motor milestones			
Time from gaining WHO motor development milestone to permanent loss of milestone ability: - Loss of the ability to sit without support - Loss of the ability to stand without support - Loss of the ability to walk without support	Time from gaining WHO motor development milestone to permanent loss of milestone ability: - Loss of the ability to sit without support - Loss of the ability to stand without support - Loss of the ability to walk without support	Time from gaining WHO motor development milestone to permanent loss of milestone ability: - Loss of the ability to walk without support	Time from gaining WHO motor development milestone to permanent loss of milestone ability: - Loss of the ability to walk without support
Motorfunction Tests			
Change from baseline in CHOP-INTEND total score at 12, 24 and 36 months after treatment start*	Change from baseline in CHOP-INTEND total score at 12, 24 and 36 months after treatment start*	Change from baseline in HFMSE total score at 12, 24, 36 months after treatment start** Change from baseline in RULM total score at 12 and 24 months after treatment start***	Change from baseline HFMSE total score 12, 24, 36 months after treatment start** Change from baseline in RULM total score at 12 and 24 months after treatment start***
Walking performance endpoints			
		-	**For ambulatory patients:** Relative change from baseline in walking distance at 12, 24 and 36 months after treatment start# Evaluation of the total walking distance at

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Overall Survival and event free survival			
			month 36 after treatment start[#]
Bulbary function			
Proportion of patients with age-appropriate Bayley III scores in the subscales “Expressive Language” and “Receptive Language” at 24 months of age Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after treatment start Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after treatment start	Proportion of patients with age-appropriate Bayley III scores in the subscales “Expressive Language” and “Receptive Language” at 24 months of age Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after treatment start Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after treatment start	Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after treatment start Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after treatment start	Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after treatment start Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after treatment start
Orthopedic complications			
Time to first documentation of scoliosis or orthopedic surgery Time to first documentation of scoliosis Time to first documentation of orthopedic surgery	Time to first documentation of scoliosis or orthopedic surgery Time to first documentation of scoliosis Time to first documentation of orthopedic surgery	Time to first documentation of scoliosis or orthopedic surgery Time to first documentation of scoliosis Time to first documentation of orthopedic surgery	Time to first documentation of scoliosis or orthopedic surgery Time to first documentation of scoliosis Time to first documentation of orthopedic surgery
Hospitalizations			
Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration	Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)	Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)	Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)

CHOP-INTEND = Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders, HFMSE = Hammersmith Functional Motor Scale Expanded, *As part of the regular SMArtCARE guidelines the CHOP-INTEND is used for follow-up monitoring of the following patients: Children: All children < 2 years of age; All patients > 2 years of age without ability to sit. Adults: For patients without ability to sit, **As part of the regular SMArtCARE guidelines the HFMSE I used for follow-up monitoring of the following patients: Children > 2 years for all patients with ability to sit; If CHOP INTEND score >50: CHOP INTEND and HFMSE; If CHOP INTEND

score >60: HFMSE instead of CHOP INTEND. Adults: All patients with ability to sit, *** As part of the regular SMArtCARE guidelines for follow-up monitoring the RULM is used for follow-up monitoring of the following patients: Children > 2 years and adults: For all patients with ability to sit in a wheelchair (see SMArtCARE: Recommendations for the evaluation of adult patients with SMA), #As part of the regular SMArtCARE guidelines for follow-up monitoring used for the following patients: > 2 years for all patients with ability to walk

Table 5: Operationalization of secondary endpoints in SMArtCARE eCRF

Variable	Fields of SMArtCARE eCRF
Secondary Variables (as applicable)	
Time to death	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN (Date of treatment) • End of data collection: Date of death
Time to permanent ventilation (two consecutive documentations of permanent ventilation of >16 hours/day)	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Start of ventilator use • Medical assessment: Ongoing use of ventilator? • Medical assessment: End of ventilator use • Medical assessment: Time of ventilator use = Continuous (>16h/day)
Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day)	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • End of data collection: Date of death • Medical assessment: Visit date • Medical assessment: Start of ventilator use • Medical assessment: Ongoing use of ventilator? • Medical assessment: End of ventilator use • Medical assessment: Time of ventilator use = Continuous (>16h/day)
Time to any respiratory support	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Does the patient receive ventilator support? • Medical assessment: Type of ventilation o Non-invasive o Invasive
Time from first treatment to reaching the WHO motor development milestone “sitting without support”	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Best current motor function = Sitting or higher current motor function • Medical assessment: Age gained of new motor milestone • Medical assessment: Age at visit (if age gained of new motor milestone not filled)
Time from first treatment to reaching the WHO motor	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment)

development milestone "standing without support"	• Medical assessment: Best current motor function = Standing without support or higher current motor function • Medical assessment: Age gained of new motor milestone • Medical assessment: Age at visit (if age gained of new motor milestone not filled)
Time from first treatment to reaching the WHO motor development milestone "walking without support"	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Best current motor function = Walking without support • Medical assessment: Age gained of new motor milestone Medical assessment: Age at visit (if age gained of new motor milestone not filled)
Time from gaining WHO motor development milestone to permanent loss of milestone ability: • Loss of the ability to sit without support • Loss of the ability to stand without support • Loss of the ability to walk without support	• Medical assessment: Best current motor function • Medical assessment: Changes in motor milestones • Medical assessment: Age gained of new motor milestone • Medical assessment: Age loss of previous motor milestone • Medical assessment: Age at visit (if age gained/loss of motor milestone not filled)
Change from baseline in CHOP INTEND total score at 12, 24 and 36 months after treatment start	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • CHOP-INTEND: Date of evaluation CHOP-INTEND: Score
Change from baseline in HFMSE total score at 12, 24 and 36 months after treatment start	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • HFMSE: Date of assessment • HFMSE: Extended Total HFMSE
Change from baseline in RULM total score at 12 and 24 months after treatment start	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • RULM: Date of assessment • RULM: Total RULM score
For ambulatory patients: relative change from baseline in walking distance at 12, 24 and 36 months after treatment start	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Walk test: Date of assessment • Walk test: distance_na
For ambulatory patients: Evaluation of the total walking distance at month 36 after treatment start	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Walk test: Date of assessment • Walk test: distance_na
Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after treatment start	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Swallowing? = With difficulties • Medical assessment: Does the patient use a gastric or nasal feeding tube? = Yes - exclusively fed by tube

	• Medical assessment: Does the patient use a gastric or nasal feeding tube? = Yes – supplementary e.g. for fluids. • Medical assessment: Start of tube feeding (date) • Medical assessment: Visit date (if start of feeding tube not filled).
Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after treatment start	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Does the patient use a gastric or nasal feeding tube? = Yes - exclusively fed by tube • Medical assessment: Does the patient use a gastric or nasal feeding tube? = Yes – supplementary e.g. for fluids • Medical assessment: Start of tube feeding (date) • Medical assessment: Visit date (if start date of feeding tube not filled)
Proportion of patients with age-appropriate Bayley III scores in the subscales “Expressive Language” and “Receptive Language” at 24 months of age	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Bayley: Date of Evaluation • Bayley: Expressive Language • Bayley: Receptive Language
Time to first documentation of scoliosis or orthopedic surgery	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Does the patient have scoliosis? • Medical assessment: Orthopedic surgery since last visit?
Time to first documentation of scoliosis	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Does the patient have scoliosis?
Time to first documentation of orthopedic surgery	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Orthopedic surgery since last visit?
Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Planned hospitalization since last visit (except for treatment administration)? • Medical assessment: Admission date • Nusinersen/onasemnogene abeparvovec; Care setting = Inpatient (overnight)? Note: Onasemnogene abeparvovec is exclusively administered in an inpatient setting in Germany. SMArtCARE CRF accordingly refers to the hospitalization for treatment. One planned hospitalization is counted for each patient receiving onasemnogene abeparvovec at the date of treatment.

8.3.3 Safety Variables

In the SMArtCARE eCRF there is no specific field for the documentation of serious adverse events. Instead, there is an option to document adverse events that lead to unplanned or prolonged hospitalization. Further, seriousness can be documented in a free text field. For this study the “adverse events that lead to unplanned or prolonged hospitalization” are used to approximately represent serious adverse events. Additional criteria for “serious adverse events” are: Adverse events leading to death, life-threatening adverse events, adverse events leading to permanent or serious disability or invalidity, medically significant, development of a congenital anomaly or birth defect.

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Proportion of patients with a SAE Proportion of patients with an AE leading to hospitalization Proportion of patients with a selected SAEs[a]	Number of AE leading to hospitalization over time Proportion of patients with a SAE Proportion of patients with an AE leading to hospitalization Proportion of patients with a selected SAEs[a]	Number of AE leading to hospitalization over time Proportion of patients with a SAE Proportion of patients with an AE leading to hospitalization Proportion of patients with a selected SAEs[a]	Number of AE leading to hospitalization over time Proportion of patients with a SAE Proportion of patients with an AE leading to hospitalization Proportion of patients with a selected SAEs[a]

[a] selected SAEs are: retinopathy, effect on epithelial tissue, thrombocytopenia, nephropathy, hydrocephalus, hepatopathy, cardiac events, sensory neuropathy

Table 6: Operationalization of safety endpoints in SMArtCARE eCRF

Variable	Fields of SMArtCARE eCRF
Safety Variables	
Number of AE leading to hospitalization over time	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Adverse events: Date recorded • Adverse events: Has there been any adverse event since the last visit? • Adverse events: Has there been unplanned or prolonged hospitalization? • Adverse events: Start date
Proportion of patients with a SAE	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Adverse events: Date recorded • Adverse events: Has there been any adverse event since the last visit? • Adverse events: Has there been unplanned or prolonged hospitalization? • Adverse event: Start date • Adverse event: Description of adverse event

Variable	Fields of SMArtCARE eCRF
Safety Variables	
Proportion of patients with an AE leading to hospitalization	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Adverse events: Date recorded • Adverse events: Has there been any adverse event since the last visit? • Adverse events: Has there been unplanned or prolonged hospitalization? • Adverse event: Start date
Proportion of patients with a selected SAE (each of the of the following): • retinopathy • effect on epithelial tissue • thrombocytopenia • nephropathy • hydrocephalus • hepatopathy • cardiac events • sensory neuropathy	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Adverse events: Date recorded • Adverse events: Has there been any adverse event since the last visit? • Adverse events: Has there been unplanned or prolonged hospitalization? • Adverse events: Any unexpected events without hospitalization? • Adverse events: Type of unexpected event • Adverse events: Start date • Adverse event: Description of adverse event

8.4 DATA SOURCE(S)

8.4.1 Collection of Data on the CRF

All clinical data for this project is collected in the SMArtCARE registry. Study site personnel is responsible for patient data collection and data entry into SMArtCARE. Data will be entered into electronic case report forms (eCRFs) of the SMArtCARE registry as timely as possible (see also SMArtCARE protocol (9)).

At enrollment and baseline the SMA confirmation including the genetic details (*SMN2* copy numbers) are documented together with date of birth and gender. The following baseline data are documented: pre-symptomatic /age at onset of symptoms, motor function, pulmonary function, nutrition, scoliosis surgery in the past, other medical history, (previous) treatment of SMA, participation in clinical studies currently/in the past.

At each visit a detailed medical assessment will be performed and documented in the eCRF giving also details on the SMA treatment and other concomitant medication. In addition, the adverse events eCRF will be completed at each visit. The eCRF pages documenting the main inclusion criteria, and effectiveness and safety variables are given in the following table.

Special documentation is available for administration of nusinersen and onasemnogene abeparvovec.

Table 7: CRF pages documenting the main inclusion criteria and effectiveness and safety variables

Variable	**eCRF page**
Main inclusion criterion	
Pre-symptomatic diagnosis / no pre-symptomatic diagnosis	Baseline – Results of the genetic examination Baseline – Clinical diagnosis
Onset of symptoms < 6 months Onset of symptoms > 6 months and < 18 months Onset of symptoms > 18 months	Baseline – Clinical diagnosis
Never achieved ability to sit unaided Never achieved ability to walk unaided Patient is able to walk unaided OR was able to walk unaided but has lost that ability	Baseline– Clinical diagnosis
SMN2 copy number is ≤ 3	Baseline– Results of the genetic examination
Primary effectiveness variables	
AE leading to hospitalization	–Adverse events
Time to death or time to permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day)	Adverse events / End of data collection Medical assessment – Pulmonary function and support
RULM total score	Physiotherapeutic evaluation - RULM
Secondary effectiveness variables	
WHO motor development milestones	Medical assessment
HFMSE score	Physiotherapeutic evaluation - HFMSE
CHOP INTEND score	Physiotherapeutic evaluation - CHOP INTEND
Bayley score	Physiotherapeutic evaluation – Bayley Scale
Respiratory support	Baseline and Medical assessment– Pulmonary function and support
Swallowing function	Medical assessment - Nutrition
Non-oral nutritional support	Baseline and Medical assessment - Nutrition
Scoliosis	Medical assessment - Orthopedic symptoms
Orthopedic surgery	Baseline and Medical assessment - Orthopedic symptoms
Walking distance	Walk test - „distance_na“ (Total distance)
Hospitalizations	Medical assessment - Hospitalization
Safety variables	
Adverse events	Adverse events

Variable	eCRF page
Treatment of SMA	Medical assessment– Medication

8.4.2 Safety Data Collection

All adverse events and serious adverse will be collected at every visit and documented in the CRF in a specific AE section. For regular follow-up patients adverse events include events with unplanned or prolonged hospitalization and additionally unexpected events without hospitalization.

For specific medications, selected AE will be collected, e.g. possible treatment-related medical occurrences such as lumbar puncture associated AE.

Death will be documented in the “End of data collection” CRF.

8.5 SAMPLE SIZE

Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene.

The current evidence for pre-symptomatic patients treated with risdiplam, nursinersen or onasemnogene abeparvovec is still limited. There is no evidence to date, for making assumptions on differences between treatments. It is therefore not possible to calculate the sample size yet.

The primary endpoint for pre-symptomatic patients is the number of AE leading to hospitalization over time. A negative binomial regression model will be used to estimate the rate ratio. Based on the first interim analyses (see section 8.7.5), the sample size for a shifted null hypothesis (RR ≥ 0,5), an one-sided alpha of 2.5% and a power of 80% will be calculated using the observed effect size.

Symptomatic patients with a clinically diagnosed SMA type 1:

For patients with a clinically diagnosed SMA type 1, the sample size estimation is based on the endpoint time to death or permanent ventilation.

The probability of the event death or permanent ventilation of patients treated with nusinersen is assumed to be 40 %, while the probability for patients treated with onasemnogene abeparvovec is assumed to be 9 % (10). Since the distribution between patients receiving nusinersen and patients receiving onasemnogene abeparvovec is not yet known, assumptions for the probability of the comparison arm cannot be derived. It is therefore not possible to calculate the sample size yet.

Based on the first interim analyses (see section 8.7.5), the sample size for a shifted null hypothesis (HR ≥ 0,5), an one-sided alpha of 2.5% and a power of 80% will be calculated using the observed effect size.

Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene

In the population of patients with clinically diagnosed SMA type 2, sample size estimation is based on the endpoint change from baseline in RULM total score.

Based on the CHERISH study, one can expect a change from baseline to month 12 of 3.7 points in the RULM total score for patients treated with Nusinersen (10), but there is no data available for the change from baseline to month 36. At the time of submission, there is no data published showing the performance in RULM total score for onasemnogene abeparvovec. Further, the distribution between patients receiving nusinersen and patients receiving onasemnogene abeparvovec is not yet known. It is therefore not possible to calculate the sample size yet.

Based on the first interim analyses (see section 8.7.5), the sample size for a shifted null hypothesis (Cohen's d ≤ 0,5), an one-sided alpha of 2.5% and a power of 80% will be calculated using the observed effect size. The threshold was chosen with regard to Cohen's rule of thumb for interpreting results (Medium Effect = 0.5) (11).

Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene

Currently data available on SMA type 3 patients treated with Nursinersen or onasemnogene abeparvovec is not sufficient to calculate the sample size.

The primary endpoint for the pre-symptomatic patients is the change from baseline in RULM total score. Based on the first interim analyses, the sample size will be calculated for a shifted null hypothesis (Cohen's d ≤ 0,5), an one-sided alpha of 2.5% and a power of 80% using the observed effect size.

8.6 DATA MANAGEMENT

Following the extraction from the data source, anonymized data will be stored at Chrestos Concept GmbH & Co. KG (named Chrestos in the following). Access to the data will be restricted to members of Chrestos. No personal data will be provided to Roche/Genentech.

8.6.1 Data Quality Assurance

Data used for this study is collected and stored in the SMArtCARE registry.

The clinical sites are responsible for implementing and maintaining quality assurance and quality control systems with written SOPs. Data are entered at the site into an eCRF as timely as possible. The clinical database is provided by OpenApp. SMArtCARE uses SAS software to review the data for completeness, consistency and plausibility. Patient data is validated by automated checks, which are specified beforehand, and manual checks by clinical monitors. Query lists are sent to the investigator who corrects data directly in the eCRF (see SMArtCARE protocol (9)). All programs which can be used to influence data or data quality are validated. The Sponsor will emphasize to investigators the importance of collecting complete data, both for outcome measures and for the confounder variables at baseline. On-site monitoring by clinical research associates will be performed at each site to improve data quality and completeness. Monitoring reports will be written for each visit and will include all findings and the expected corresponding corrections and changes.

Implausible data will further be assessed in Data Review Meetings conducted before each status report, interim analysis and final analysis. In this meeting the handling of implausible data and outliers will be discussed and documented.

8.6.2 Electronic Case Report Forms

SMArtCARE uses an electronic data capture (EDC) system. This system is implemented and maintained by Open Applications Consulting Ltd. SAS software is used to review the data for completeness, consistency and plausibility. Query resolution processes are implemented. All programs which can be used to influence data or data quality are validated (e.g. data validation programs, programs for CRF/query tracking, programs for import of EDC data into SAS or for import of external data, etc.).

8.6.3 Source Data Documentation

Source data verification (SDV) is performed by SMArtCARE according to protocol in order to verify the accuracy and completeness of the entries on the eCRF by comparing them with the source data, and to ensure and increase the quality of the data (SMArtCARE protocol).

In addition, SDV for 100% of patients for the primary endpoint and for at least 10% of randomly selected patients for all other endpoints over the period since the start of data collection will be performed by Clinische Studien Gesellschaft (CSG).

8.7 DATA ANALYSIS

All analyses are based on the Full Analysis Set (FAS), including all enrolled patients. The participants will be included in the analyses according to the treatment they received at enrollment. If an initial therapy is documented for less than three months followed by an alternative therapy , the patient is allocated to the treatment of the following therapy (7).

The index date for each patient will be the date of the therapy decision. If the therapy decision was not documented, the index date will be the date of the first treatment administration (of the treatment the patient was allocated to). Relevant confounders have been specified according to the description in Section 8.7.4. To adjust for differences in the confounder variables between the treatment groups, propensity score weighting will be applied if sufficient overlap and balance between the scores is given. Depending on the amount of missing data for the confounder variables, a complete case analysis or multiple imputation prior to propensity score calculation are considered according to the rules defined in the statistical analysis plan (SAP).

8.7.1 Primary Objectives Analyses

All primary estimands will be evaluated following the treatment-policy strategy to handle intercurrent events (e.g. early discontinuation from the study treatment or treatment switch). Additionally, supplementary estimands with the hypothetical strategy will be investigated as well, as described in the SAP. Sensitivity analyses will be conducted as described in the SAP to assess the heterogeneity in the control arm and the use of prospective and retrospective enrolled patients in a pooled analysis. For hypothesis testing, statistical significance is controlled at the 1-sided, 0.025 alpha level and the shifted null hypothesis. Point estimators will be presented with 2-sided 95% confidence intervals.

The comparison of the number of AE leading to hospitalization over time between the arms will be performed using a negative binomial regression model, which accounts for different follow-up times, with the patient's number of AE leading to hospitalization as a function of treatment arm and the time that each patient stays in the hospital included as an offset in the model. This analytic model estimates the rate ratio, which quantifies the risk of AE leading to hospitalization associated with risdiplam in comparison to the control arm.

Time to death or permanent ventilation will be presented graphically using Kaplan-Meier curves and with the median and 25% quantiles. To quantify the treatment effect, the hazard ratio (and the 2-sided 95% confidence interval (CI) will be estimated.

For the change from baseline of RULM total score, a MMRM analysis will be performed. With the estimated means and standard deviations, Cohen's d will be estimated as a measure of the effect size via $d = \frac{M_1 - M_2}{SD_{pooled}}$. The estimated treatment difference in the

mean change from baseline will be presented with a 95% CI and the p-value will be presented based on a 1-sided t-test. The score and change from baseline score will also be summarized using descriptive statistics. The mean absolute scores and change from baseline scores over time will also be presented graphically using a line plot.

8.7.2 Safety Analyses

The analysis of safety outcomes/variables is based on all SAE, AE leading to hospitalization and selected SAE. The number and percentage of patients with a (serious) adverse event in each category will be summarized and compared using relative and absolute effect measures, including absolute risk reduction, odds ratio and relative risk

All SAE, AE leading to hospitalization and selected SAE term entered by the physician describing the event (the “verbatim term”) will be assigned to a standardized term (the “preferred term”) based on the most up-to-date version of Medical Dictionary for Regulatory Activities (MedDRA). Summary statistics of SAE, AE leading to hospitalization and selected SAE will be performed using preferred terms and their according system organ class.

Follow-up times will be evaluated in the Data Review Meeting before the final analysis to investigate if time to event analyses are more appropriate for all SAE, AE leading to hospitalization and selected AE than responder analyses.

The proportion of patients with SAE, AE leading to hospitalization and selected SAE will be summarized according to the preferred term and their according system organ class.

The number of AE leading to hospitalization over time will be analyzed separately using negative binomial regression models.

8.7.3 Subgroups

Subgroup analyses will be performed to investigate the generalizability of the results when comparing risdiplam to the control arm as described in the SAP. Analyses will be presented for the following subgroups:

Table 8: Subgroups

Subgroups	Categories	Populations
Sex	Male, female	All
Age at treatment initiation	0 to 18 months, 18 months to 5 years, 6 to 11 years, 12 to 17 years, and 18 to 25 years, > 25 years	All
Geographic region	Germany, Austria	All
History of scoliosis surgery	Yes, no	SMA2, SMA3

Highest motor milestone at baseline (disease severity)	None, Sitting without support, Crawl on hands and knees, Standing without support, Walking without support, Climb stairs	All
Nutrition support	Yes – exclusively, yes – supplementary, no	All
Ventilation support	Yes, no	All
Contractures	Yes, no	SMA1, SMA2, SMA3
SMN2 Copy Number	1, 2, 3	All
Baseline CHOP-INTEND	≤ median score, > median score[a]	SMA1, presymptomatic
Baseline HFMSE score	≤ median score, > median score	SMA2, SMA3
Baseline CMAP amplitude	<1.5mV, ≥1.5mV	presymptomatic
Time between first treatment and onset of symptoms	≤ 3 months, > 3 months	SMA1

[a] in accordance with the real world data collection for the reassessment of the additional benefit of onasemnogene abeparvovec

8.7.4 Confounder

For the real world data collection for the reassessment of the additional benefit of risdiplam all confounders should be identified in advance through a systematic research and prespecified for the analyses.

The Institute for Quality and Efficiency in Health Care (IQWiG) issued a rapid report on May 13, 2020, titled "Concepts for the generation of data in health care settings and their evaluation for the purpose of assessing the benefit of drugs according to § 35a SGB V," version 1.1. This document offers guidance on how to analyze patient-specific data within the context of drug benefit assessments under § 35a SGB V. IQWiG addresses crucial elements such as the planning of studies and statistical analyses, as well as the significance of accounting for confounders in studies that are not randomized. The report stresses the need for a priori definition of confounders based on scientific literature and, where necessary, their validation by clinical experts. Accordingly, a systematic literature review (SLR) was performed to identify potential confounders for SMA, outlined in national and international guidelines, recommendations, and publications, and validated them with clinical experts, ensuring compliance with the evidence development requirements in Germany.

The results and the used methodology to identify confounder via a systematic literature review and validation by clinical experts are described in detail in the final report of the systematic confounder research (12).

Clinical experts categorized the identified confounders into three groups:
Very Important: Essential for adjusting non-randomized studies to ensure validity.
Less Important: Marginally affect outcomes but not critical to study validity.
Not Important: Irrelevant to the study due to specific characteristics.

The following rules were applied to select which potential confounders and characteristics will be used during data analysis:

- Confounders which were classified as “not important” will not be used during data analysis.
- All potential confounders which are classified as “very important” will be used for analysis. Except for “Presymptomatic/symptomatic at onset” which is already a stratification factor.
- If there is more than one “characteristic” found for one potential confounder, the most important one is used. In case there are several “characteristics” with the same level of importance the same characteristic will be used as in the protocol of onasemnogene abeparvovec.
- “Less important” will be used in case it is required by the IQWiG or it is used in the protocol of onasemnogene abeparvovec.

Table 9: Confounders

Confounder	Type of variabel	Clinical relevance [a]	Definition	Operationalization in SMArtCARE eCRF	Applicable to analysis population
SMN2 copy number	Discrete	Very important	SMN2 copy number	Genetic Test Result: SMN2 copy number	All
Age at symptom onset	Continuous	Less important	Age of symptom onset in months for symptomatic patients	Clinical Diagnosis: Age at symptom onset	SMA type 1, SMA type 2, SMA type 3
Age at treatment initiation	Continuous	Very important	Age in weeks at treatment initiation	Registries, Clinical Trials: Age at visit AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene	Pre-symptomatic patients: directly SMA type 1, SMA type 2, SMA type 3: Derived (treatment delay defined as time from symptom onset

Confounder	Type of variabel	Clinical relevance [a]	Definition	Operationalization in SMArtCARE eCRF	Applicable to analysis population
				abeparvovec: MIN(Date of treatment)	to treatment initiation)
Early diagnosis	Discrete	Very important	Neonatal screening and early diagnosis	Baseline characteristics, newborn screening	All
Nutrition support	Discrete	Very important	Gastric tube or nasal feeding tube (exclusive/ supplemental/ no ne) at treatment initiation	Nutrition: Does the patient use a gastric or nasal feeding tube? AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN(Date of treatment)	SMA type 1, SMA type 2, SMA type 3
Ventilation support	Discrete	Very important	Duration of ventilator use (nighttime/intermittent/ permanent (≥16h/day) at treatment initiation	Pulmonary: Does the patient receive ventilator support? = Yes AND Pulmonary: Time of ventilator use 1. Night (during sleep) 2. Intermittent day time and continuous at night 3. Continuous (>16h/day) AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	SMA type 1, SMA type 2, SMA type 3
Contractures	Discrete	Less important	Contractures limiting function (yes/no) at treatment	Clinical Examination: Are any contractures present? = Yes	SMA type 1, SMA type 2, SMA type 3

Confounder	Type of variabel	Clinical relevance [a]	Definition	Operationalization in SMArtCARE eCRF	Applicable to analysis population
			initiation	AND Registries, Clinical Trials: Type of limitation = Severe (imposing limits to function) AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	
Motoric function: Highest motor milestone (at treatment initiation)	Discrete	Very important	Highest motor milestone at treatment initiation: None/n.a. Sitting without support Crawl on hands and knees Standing without support Walking without support Climb stairs	Best current motor function: Best current motor function AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	SMA type 2, SMA type 3
Motoric Function CHOP-INTEND	Discrete	Very important	CHOP-INTEND score at treatment initiation	CHOP-INTEND: Score AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	All
Motoric Function: HFMSE score	Discrete	Very important	Mean Hammersmith score treatment initiation	HFMSE: total AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene	SMA type 1, SMA type 2 SMA type 3

Confounder	Type of variabel	Clinical relevance [a]	Definition	Operationalization in SMArtCARE eCRF	Applicable to analysis population
				abeparvovec: MIN (Date of treatment)	
Physical activity	Discrete	Less important	Physiotherapy		SMA type 1, SMA type 2
Multiple disorders	Discrete	Less important	Multiple disorders	Medical history	SMA type 1, SMA type 2, SMA type 3

[a] Depiction of assessment from advising clinical experts and not subject to any input from Roche Pharma AG. Categorization of “less important” vs. “very important” does not influence depiction or handling of confounder in statistical analysis.

All confounder variables will be included in the propensity score model as indicated by their type (continuous, discrete), as long as the criteria regarding the amount of missing data as specified in the SAP is fulfilled.

8.7.5 Planned interim analyses and status reports

First status report (submission 6 months after study start):

Disposition, summaries of demographics / baseline characteristics, exposure and patient-related observation period will be analyzed as described in the SAP and will be presented in the status report. Further analyses might be conducted and presented if appropriate. The data cut for this analysis will be at study start (retrospective enrolled patients and, if possible, prospective enrolled patients).

Second status report and first interim analysis (submission 18 months after study start):

Disposition, summaries of demographics / baseline characteristics, exposure and patient-related observation period will be analyzed as described in the SAP. The primary endpoints (and secondary endpoints if appropriate) will be analyzed as described in the SAP. Module 4 of the dossier template will be used to submit the results. Based on this interim analysis, the sample size will be calculated using observed effect sizes and recruitment rates as assumptions. If the expected power is less than 60% for a primary endpoint (and relevant secondary endpoints) the enrollment might be stopped due to futility in the respective population. The data cut for this analysis will be 12 months after study start.

Third status report and second interim analysis (submission 30 months after study start):

Disposition, summaries of demographics / baseline characteristics, exposure and patient-related observation period will be analyzed as described in the SAP. The primary endpoints (and secondary endpoints if appropriate) will be analyzed as described in the SAP. Module 4 of the dossier template will be used to submit the results. If the expected

power is less than 60% for a primary endpoint (and relevant secondary endpoints) the enrollment might be stopped due to futility in the respective population. The data cut for this analysis will be 24 months after study start.

8.8 DATA QUALITY ASSURANCE AND QUALITY CONTROL

The Marketing Authorization Holder (MAH) must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, and documentation of Institutional Review Board/Ethics Committee (IRB/EC) and governmental approval/notification (if necessary).

Chrestos, a Contract research Organization (CRO) commissioned by MAH, shall ensure that the datasets and statistical programs used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

Data not held within MAH systems will be periodically transferred electronically from SMArtCARE registry to Chrestos. SMArtCARE registry will comply with the MAH procedures as written in the contract regarding content, archiving and records management of process documents.

Retention of Records

Archiving at the study site has to be for at least five years after final study report or first publication of study results, whichever comes later; or according to local regulation.

Records and documents pertaining to the conduct of this study must be retained by SMArtCARE for at least 25 years after completion of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the SMArtCARE. Written notification should be provided to the SMArtCARE prior to transferring any records to another party or moving them to another location.

8.9 LIMITATIONS OF THE RESEARCH METHOD

As any observational research this study is subject to a risk of bias. The data collected in this study is dependent on routine clinical practice and the level of data collected may differ between participating sites. Consequently, the data obtained in this study will be less comprehensive than data obtained from a prospective, interventional clinical study.

To minimize the bias, certain measurements will be performed (detailed description in the SAP). Missing confounder values will be addressed (complete case, multiple imputation or exclusion of variables). Propensity score weighting will be applied to adjust for differences in the confounder variables between the treatment groups. Data reporting will be conducted in a consistent way to avoid bias in the data collection process.

9. PROTECTION OF HUMAN PATIENTS

Data will be collected as part of routine clinical practice. The responsibility lies with the treating physician.

9.1 INFORMED CONSENT

The patients have explicitly agreed to any secondary use of their data.

9.2 CONFIDENTIALITY

The SMArtCARE registry maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in datasets that are transmitted to any SMArtCARE registry location. Only aggregated data from the registry are available and are used in this study.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, CSG monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

9.3 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for Good Pharmacoepidemiological Practice (GPP) published by the International Society of Pharmacoepidemiology (ISPE) and the laws and regulations of the country in which the research is conducted.

9.4 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol and relevant supporting information must be submitted to the EC, and reviewed and approved by the EC before the study is initiated.

SMArtCARE is responsible for providing written summaries of the status of the study to the EC annually or more frequently in accordance with the requirements, policies, and procedures established by the EC.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS

All adverse events extracted from the data source for the study as specified in the protocol will be summarized as part of any interim analyses and in the final value dossier submission in scope of the reassessment of the additional benefit of risdiplam by G-BA (4).

11. PLANS FOR DISSEMINATION AND COMMUNICATION OF STUDY RESULTS

Study results will be published in scope of the reassessment of the additional benefit of risdiplam by G-BA (4).

12. REFERENCES

1. Roche. Beratungsantrag zum Wirkstoff Risdiplam in dem Anwendungsgebiet Spinale Beratungsantrag zum Wirkstoff Risdiplam in dem Anwendungsgebiet Spinale Muskelatrophie - Anwendungsbegleitende Datenerhebung; 19.8.2022.
2. G-BA. Niederschrift (finale Fassung) zum Beratungsgespräch gemäß § 8 AM-NutzenV Beratungsanforderung 2022-B-215 Risdiplam zur Behandlung der 5q-assiziierten spnalen Muskelatrophie (SMA); 28.11.2022.
3. IQWiG. A21-131 - Anwendungsbegleitende Datenerhebung Risdiplam - Rapid Report - Version 1.0: Stand: 15.02.2022; 2022.
4. G-BA. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Risdiplam (spinale Muskelatrophie); Forderung einer anwendungsbegleitenden Datenerhebung und von Auswertungen: Vom 21. Juli 2022; 2022.
5. G-BA. Zusammenfassende Dokumentation über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Risdiplam (Spinale Muskelatrophie) Forderung einer anwendungsbegleitenden Datenerhebung und von Auswertungen; 21.7.2022.
6. G-BA. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über die Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Risdiplam (spinale Muskelatrophie); Forderung einer anwendungsbegleitenden Datenerhebung und von Auswertungen: Vom 21. Juli 2022; 2022.
7. Proud CM, Mercuri E, Finkel RS, Kirschner J, Vivo DC de, Muntoni F et al. Combination disease-modifying treatment in spinal muscular atrophy: A proposed classification. Ann Clin Transl Neurol; 10(11):2155–60, 2023. doi: 10.1002/acn3.51889.
8. G-BA. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Feststellung im Verfahren der anwendungsbegleitenden Datenerhebung und von Auswertungen nach § 35a Absatz 3b des Fünften Buches Sozialgesetzbuch (SGB V): Risdiplam (spinale Muskelatrophie) – Vorlage von Studienprotokoll und Statistischem Analyseplan; 2024.
9. Dr. Astrid Pechmann. Longitudinal Data Collection from Patients with Spinal Muscular Atrophy: The SMArtCARE Database: Study protocol v2.1, 2022.
10. Ribero VA, Daigl M, Martí Y, Gorni K, Evans R, Scott DA et al. How does risdiplam compare with other treatments for Types 1-3 spinal muscular atrophy: a systematic literature review and indirect treatment comparison. J Comp Eff Res; 11(5):347–70, 2022. doi: 10.2217/cer-2021-0216.

11. Jacob Cohen, Hrsg. Statistical Power Analysis for the Behavioral Sciences (Revised Edition): The t Test for Means; 1988.
12. Berkemeier F. Systematic identification and validation of potential confounders Patients with an indication of Spinal Muscular Atrophy (SMA), 2024.

STATISTICAL ANALYSIS PLAN

STUDY TITLE:	**EVALUATION OF A REAL WORLD DATA COLLECTION FOR THE REASSESSMENT OF THE ADDITIONAL BENEFIT OF EVRYSDI® (RISDIPLAM)**
STUDY NUMBER:	ML44661
VERSION NUMBER:	3.0
ROCHE COMPOUND(S):	EVRYSDI® (RISDIPLAM)
PLAN PREPARED BY:	[redacted]

STATISTICAL ANALYSIS PLAN APPROVAL

Sponsor Signature(s) and Date(s):

[redacted]

MARKETING AUTHORIZATIONHOLDER (MAH):	Roche Registration GmbH
LEGAL REGISTERED ADDRESS:	Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany
DATE FINAL:	See electronic date stamp above

STATISTICAL ANALYSIS PLAN VERSION HISTORY

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
1	10-Aug-2023	1.0, 31-Jul-2023
2	02-May-2024	2.0; 02-May-2024
3	see electronic date stamp on title page	3.0; 25-Jun-2024

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

Initial version.

TABLE OF CONTENTS

LIST OF TABLES

Es konnten keine Einträge für ein Abbildungsverzeichnis gefunden werden.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
AE	adverse event
AR	autoregressive
BSID	Bayley scale of infant development
CHOP-INTEND	Children's hospital of Philadelphia infant test of neuromuscular disorders
eCRF	electronic case report form
EDC	electronic data capture
FAS	full analysis set
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HFMSE	Hammersmith functional motor scale expanded
HR	hazard ratio
ICH	International Council on Harmonization
IPTW	inverse probability of treatment weights
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MICE	multiple imputation by chained equations
MMRM	mixed model repeated measures
NBS	newborn screening
RULM	Revised upper limb module
SAE	serious adverse events
SAP	Statistical Analysis Plan
SD	standard deviation
SDV	source data verification
SMA	spinal muscular atrophy
SMN 1/2	survival motor neuron 1/2
SmPC	summary of product characteristics
SOP	standard operating procedures
WHO	World health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical analysis of the data collected within the framework of study ML44661. It is based on the final study protocol, version 3.0, dated 24 Jun 2024 and follows the principles of the Guideline ICH E9. It gives all details for the statistical analysis of this study. The statistical analysis will be carried out according to Chrestos standard operating procedures (SOP).

The SAP contains a more technical and detailed elaboration of the procedures described in the study protocol for conducting the statistical analyses.

This SAP was written and finalized prior to database hard lock and data analysis.

Spinal muscular atrophy (SMA) is a rare autosomal recessive neuromuscular disorder characterized by the progressive loss of proximal motor neurons leading to muscle weakness and profound neuromotor disability. It is primarily characterized by degeneration of the anterior horn cells of the spinal cord resulting in muscle atrophy and proximal muscle weakness. It is caused by a homozygous deletion in the survival motor neuron 1 (*SMN1*) gene on chromosome 5q13. The severity of the disease is highly variable and correlates with the age of onset and *SMN2* copy number. For classification purposes, patients are usually categorized into three main subtypes based on clinical criteria, including achieving (or failing to achieve) physical motor milestones, age of onset, and expected life span:

- Type 1 SMA (severe infantile type with onset before 6 months of age; infants never sit without support, with death due to respiratory distress usually within 2 years),
- Type 2 SMA (intermediate chronic infantile type with onset after the age of 6 months, children unable to stand or walk without support),
- Type 3 SMA (chronic juvenile type with onset around the age of 18 months, children able to walk until the disease progresses)

For the best possible development or preservation of motor function, it is particularly important that treatment is started as early as possible. In October 2021, the newborn screening (NBS) for SMA was therefore implemented in Germany. This will allow newborns with SMA to be diagnosed immediately after birth. One consequence of the introduction of the NBS for SMA is that fewer symptomatic patients will be diagnosed in the long term.

In all types of SMA, as the disease progresses, clinical symptoms include hypotonia, symmetrical muscle weakness and atrophy (predominantly of the proximal muscles of the shoulder and pelvic girdle), diminished or absent deep tendon reflexes, tremor of fingers and hands, fasciculation of the tongue muscles, and hyporeflexia with orthopedic deformities (contractures, scoliosis). Progressive respiratory failure and frequent pulmonary infections and superinfections are common in Types 1 and 2 SMA. Other common comorbidities include failure to thrive, pneumonia, osteopenia and osteoporosis

with pathological fractures, poor cough and secretion clearance, reduced vital capacity, gastroesophageal dysmotility, urinary incontinence, hip dislocation, and joint and muscle pain.

On the basis of the ongoing or completed studies on risdiplam considered for approval, the) identified evidence gaps, particularly comparative data of a treatment with risdiplam versus existing appropriate therapy alternatives are missing for patients.

Thus, the G-BA initiated a procedure to require an evaluation of a real world data collection for the reassessment of the additional benefit of risdiplam.

1.1 OBJECTIVES AND ENDPOINTS AND ESTIMANDS

1.1.1 Primary Objectives and corresponding Estimands

Table 1: Primary Objectives / Estimands

Primary Objective	Estimand Definition
To evaluate the safety of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as the number of adverse events (AE) leading to hospitalization over time	Population: Presymptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene as defined by the study inclusion and exclusion criteria (see protocol for details) Endpoint: Number of AE leading to hospitalization over time Treatment (see protocol for details): Experimental arm: Risdiplam according to Summary of Product Characteristics (SmPC) Control arm: Nusinersen or onasemnogene abeparvovec according to SmPC Intercurrent events and handling strategies: Early discontinuation from study treatment: Treatment-policy strategy Treatment switch: Treatment-policy strategy Population-level summary: Rate ratio
To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as time to death or permanent ventilation	Population: Symptomatic patients with a clinically diagnosed SMA type 1 (see protocol for details) Endpoint: Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Treatment: as defined above Intercurrent events and handling strategies: Early discontinuation from study treatment: Treatment-policy strategy Treatment switch: Treatment-policy strategy Population-level summary: Hazard ratio
To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec	Population: Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene (see protocol for details). Only patients with

Primary Objective	Estimand Definition
measured as change from baseline of RULM total score	a baseline value and a value at month 36 after treatment start are included. Endpoint: Change from baseline of RULM total score at 36 months after treatment start Treatment: as defined above Intercurrent events and handling strategies: Early discontinuation from study treatment: Treatment-policy strategy Treatment switch: Treatment-policy strategy Population-level summary: Cohen's d
To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as change from baseline of RULM total score	Population: Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene (see protocol for details). Only patients with a baseline value and a value at month 36 after treatment start are included. Endpoint: as defined above Treatment: as defined above Intercurrent events and handling strategies: as defined above Population-level summary: as defined above

Abbreviations; RULM = revised upper limb module

1.1.2 Secondary Objectives and Endpoints

Table 2: Secondary Endpoints

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Overall Survival and event free survival			
Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to death Time to permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to any respiratory support	Time to death Time to permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to any respiratory support	Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to death Time to permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to any respiratory support	Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to death Time to permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to any respiratory support
Achievement of WHO motor development milestones			

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Overall Survival and event free survival			
Time from first treatment to reaching the WHO motor development milestone of sitting without support Time from first treatment to reaching the WHO motor development milestone of standing without support Time from first treatment to reaching the WHO motor development milestone of walking without support	Time from first treatment to reaching the WHO motor development milestone of sitting without support Time from first treatment to reaching the WHO motor development milestone of standing without support Time from first treatment to reaching the WHO motor development milestone of walking without support	Time from first treatment to reaching the WHO motor development milestone of walking without support	-
Sustainability of motor milestones			
Time from gaining WHO motor development milestone to permanent loss of milestone ability: - Loss of the ability to sit without support - Loss of the ability to stand without support - Loss of the ability to walk without support	Time from gaining WHO motor development milestone to permanent loss of milestone ability: - Loss of the ability to sit without support - Loss of the ability to stand without support - Loss of the ability to walk without support	Time from gaining WHO motor development milestone to permanent loss of milestone ability: - Loss of the ability to walk without support	Time from gaining WHO motor development milestone to permanent loss of milestone ability: - Loss of the ability to walk without support
Motorfunction Tests			
Change from baseline in CHOP-INTEND total score at 12, 24 and 36 months after treatment start*	Change from baseline in CHOP-INTEND total score at 12, 24 and 36 months after treatment start*	Change from baseline in HFMSE total score at 12, 24, 36 months after treatment start** Change from baseline in RULM total score at 12 and 24 months after treatment start***	Change from baseline HFMSE total score 12, 24, 36 months after treatment start** Change from baseline in RULM total score at 12 and 24 months after treatment start***
Walking performance endpoints			
		-	**For ambulatory patients:** Relative change from baseline in walking distance at 12, 24 and 36 months after treatment start[#] Evaluation of the total walking distance at

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Overall Survival and event free survival			
			month 36 after treatment start[#]
Bulbary function			
Proportion of patients with age-appropriate Bayley III scores in the subscales “Expressive Language” and “Receptive Language” at 24 months of age Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after treatment start Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after treatment start	Proportion of patients with age-appropriate Bayley III scores in the subscales “Expressive Language” and “Receptive Language” at 24 months of age Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after treatment start Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after treatment start	Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after treatment start Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after treatment start	Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after treatment start Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after treatment start
Orthopedic complications			
Time to first documentation of scoliosis or orthopedic surgery Time to first documentation of scoliosis Time to first documentation of orthopedic surgery	Time to first documentation of scoliosis or orthopedic surgery Time to first documentation of scoliosis Time to first documentation of orthopedic surgery	Time to first documentation of scoliosis or orthopedic surgery Time to first documentation of scoliosis Time to first documentation of orthopedic surgery	Time to first documentation of scoliosis or orthopedic surgery Time to first documentation of scoliosis Time to first documentation of orthopedic surgery
Hospitalizations			
Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration	Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)	Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)	Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)

CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, HFMSE = Hammersmith Functional Motor Scale Expanded, *As part of the regular SMArtCARE guidelines the CHOP-INTEND is used for follow-up monitoring of the following patients: Children: All children < 2 years of age; All patients > 2 years of age without ability to sit. Adults: For patients without ability to sit, **As part of the regular SMArtCARE guidelines the HFMSE I used for follow-up monitoring of the following patients: Children > 2 years for all patients with ability to sit; If CHOP INTEND score >50: CHOP INTEND and HFMSE; If CHOP INTEND score >60: HFMSE instead of CHOP INTEND. Adults: All patients with ability to sit, * As part of the regular SMArtCARE guidelines for follow-up monitoring the RULM is used for follow-up monitoring of the following patients: Children > 2 years and adults: For all patients with ability to sit in a wheelchair (see SMArtCARE: Recommendations for the evaluation of adult patients with SMA), #As part of the regular SMArtCARE guidelines for follow-up monitoring used for the following patients: > 2 years for all patients with ability to walk**

Table 3: Safety Endpoints

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Proportion of patients with a SAE Proportion of patients with an AE leading to hospitalization Proportion of patients with a selected SAEs[a]	Number of AE leading to hospitalization over time Proportion of patients with a SAE Proportion of patients with an AE leading to hospitalization Proportion of patients with a selected SAEs[a]	Number of AE leading to hospitalization over time Proportion of patients with a SAE Proportion of patients with an AE leading to hospitalization Proportion of patients with a selected SAEs[a]	Number of AE leading to hospitalization over time Proportion of patients with a SAE Proportion of patients with an AE leading to hospitalization Proportion of patients with a selected SAEs[a]

[a] selected SAEs are: retinopathy, effect on epithelial tissue, thrombocytopenia, nephropathy, hydrocephalus, hepatopathy, cardiac events, sensory neuropathy

Abbreviations: AE – adverse event, SAE – serious adverse event

1.2 STUDY DESIGN

This study is a registry-based, comparative, non-interventional, multicentric, multinational, open-label study. As the treatment start date differs, there will be simultaneously enrolled controls and not simultaneously enrolled controls.This registry-based study is based on the data of the SMArtCARE registry. The SMArtCARE project (www.smartcare.de) provides a platform to collect longitudinal clinical routine data on SMA patients in Germany, Austria, and Switzerland.

The registry collects data from SMA patients since 2018. Retrospective data for patients treated with nusinersen will be analyzed since the beginning of the registry (May 30, 2017 at the earliest), data for patients treated with onasemnogene abeparvovec since

approval in 2020 (May 18, 2020 at the earliest) and data for patients treated with risdiplam since approval in 2021 (March 26, 2021 at the earliest). Details of the registry are given in the SMArtCARE protocol (1).

Start Date of Study:

The planned start of this study is after confirmation of the submitted study protocol and statistical analysis plan by the G-BA.

Interim Analyses

Interim analyses are planned 12 and 24 months after start of the study and will be handed in to G-BA latest after 18 and 30 months after the start of the study. Based on these interim analysis, a final sample size estimate will be made using more precise effect assumptions. Final analysis will take place in January 2026.

End of Study:

All patients in the study should generally be followed up for at least 36 months. Follow-up time can vary between patients depending on their entry date in the registry.

The planned end date is January 01, 2026. Data that is documented in the study database after that time point will not be taken into account.

1.2.1 Data Monitoring

Data used for this study are collected and stored in the SMArtCARE registry.

The clinical sites are responsible for implementing and maintaining quality assurance and quality control systems with written SOPs. Data are entered at the site into an electronic case report form (eCRF) as timely as possible. The clinical database is provided by OpenApp. SMArtCARE uses SAS software to review the data for completeness, consistency and plausibility. Patient data is validated by automated checks, which are specified beforehand, and manual checks by clinical monitors. Query lists are sent to the investigator who corrects data directly in the eCRF (see SMArtCARE protocol). All programs which can be used to influence data or data quality are validated. On-site monitoring by clinical research associates will be performed at each site to improve data quality and completeness. Monitoring reports will be written for each visit and will include all findings and the expected corresponding corrections and changes.

Implausible data will further be assessed in Data Review Meetings conducted before each status report, interim analysis and final analysis. In this meeting the handling of implausible data and outliers will be discussed and documented.

SMArtCARE uses an electronic data capture (EDC) system (1). This system is implemented and maintained by Open Applications Consulting Ltd. SAS software is used to review the data for completeness, consistency and plausibility. Query resolution processes are implemented. All programs which can be used to influence data or data

quality are validated (e.g. data validation programs, programs for CRF/query tracking, programs for import of EDC data into SAS or for import of external data, etc.).

Source data verification (SDV) is performed by SMArtCARE according to protocol in order to verify the accuracy and completeness of the entries on the eCRF by comparing them with the source data, and to ensure and increase the quality of the data (1).

In addition, SDV for 100% of patients for the primary endpoint and for at least 10% of randomly selected patients for all other endpoints over the period since the start of data collection will be performed by Clinische Studien Gesellschaft (CSG).

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

2.1 STATISTICAL HYPOTHESES

Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene.

The comparison of the number of AE leading to hospitalization over time between both arms will be performed using a negative binomial regression model. This analytic model estimates the rate ratio, λ_e / λ_c, which quantifies the risk of AE leading to hospitalization associated with risdiplam (λ_e) in comparison to nusinersen or onasemnogene abeparvovec (λ_c). Statistical significance is controlled at the 1-sided, 0.025 alpha (α) level. The Wald test will be performed via the following hypothesis:

H_0: Rate Ratio ≥ 0.5 versus H_1: Rate Ratio < 0.5

Symptomatic patients with a clinically diagnosed SMA type 1:

Treatment comparison of the time to death or permanent ventilation will be based on the Cox-regression test. Statistical significance is controlled at the 1-sided, 0.025 alpha (α) level. The shifted null and alternative hypotheses can be phrased as:

H_0: Hazard Ratio ≥ 0.5 versus H_1: Hazard Ratio < 0.5

Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the SMN2 gene:

The Change from baseline of RULM total score change from baseline endpoints a mixed model repeated measures (MMRM) analysis will be performed and Cohen's d will be estimated as a measure of the effect size. Statistical significance is controlled at the 1-sided, 0.025 alpha (α) level. The hypothesis to be tested with a t-test is that the difference in the mean change from baseline in the total RULM score at Month 36 between risdiplam and nusinersen or onasemnogene abeparvovec (δ) is:

H_0: $\delta \leq 0.5$ versus H_1: $\delta > 0.5$

Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:

See SMA type 2 and up to three copies of the *SMN2* gene.

2.2 SAMPLE SIZE DETERMINATION

Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene.

The current evidence for pre-symptomatic patients treated with risdiplam, nursinersen or onasemnogene abeparvovec is still limited. There is no evidence to date, for making assumptions on differences between treatments. It is therefore not possible to calculate the sample size yet.

The primary endpoint for pre-symptomatic patients is the number of AE leading to hospitalization over time. A negative binomial regression model will be used to estimate the rate ratio. Based on the first interim analyses (see Section 4.7.1), the sample size for a shifted null hypothesis (RR ≥ 0.5), an one-sided alpha of 2.5% and a power of 80% will be calculated using the observed effect size.

Symptomatic patients with a clinically diagnosed SMA type 1:

For patients with a clinically diagnosed SMA type 1, the sample size estimation is based on the endpoint time to death or permanent ventilation.

The probability of the event death or permanent ventilation of patients treated with nusinersen is assumed to be 40 % (2), while the probability for patients treated with onasemnogene abeparvovec is assumed to be 9 % (3). Since the distribution between patients receiving nusinersen and patients receiving onasemnogene abeparvovec is not yet known, assumptions for the probability of the comparison arm cannot be derived. It is therefore not possible to calculate the sample size yet.

Based on the first interim analyses (see Section 4.7.1), the sample size for a shifted null hypothesis (HR ≥ 0,5), an one-sided alpha of 2.5% and a power of 80% will be calculated using the observed effect size.

Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene

In the population of patients with clinically diagnosed SMA type 2, sample size estimation is based on the endpoint change from baseline in RULM total score.

Based on the CHERISH study, one can expect a change from baseline to month 12 of 3.7 points in the RULM total score for patients treated with nusinersen (4), but there is no data available for the change from baseline to month 36. At the time of submission, there is no data published showing the performance in RULM total score for onasemnogene abeparvovec. Further, the distribution between patients receiving

nusinersen and patients receiving onasemnogene abeparvovec is not yet known. It is therefore not possible to calculate the sample size yet.

Based on the first interim analyses (see Section 4.7.1), the sample size for a shifted null hypothesis (Cohen's d ≤ 0,5), an one-sided alpha of 2.5% and a power of 80% will be calculated using the observed effect size. The threshold was chosen with regard to Cohen's rule of thumb for interpreting results (medium effect = 0.5) (5).

Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene

Currently data available on SMA type 3 patients treated with nursinersen or onasemnogene abeparvovec is not sufficient to calculate the sample size.

The primary endpoint for the pre-symptomatic patients is the change from baseline in RULM total score. Based on the first interim analyses, the sample size will be calculated for a shifted null hypothesis (Cohen's d ≤ 0,5), an one-sided alpha of 2.5% and a power of 80% using the observed effect size.

3. ANALYSIS SETS

The participant analysis sets for the purposes of analyses are defined in Table 4.

Table 4 Participant Analysis Sets

Participant Analysis Set	Description
FAS	All enrolled participants; participants will be included in the analyses according to the treatment they received at enrollment. If an initial therapy is documented for less than three months followed by an alternative therapy, the patient is allocated to the treatment of the following therapy.

FAS = full analysis set

4. STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

All clinical data will be downloaded and transferred into SAS® datasets. All statistical analyses will be carried out using SAS®, version 9.4 or higher and R, version 4.3.0 or higher.

If not specified otherwise, descriptive statistics will be presented by treatment group and time point, where appropriate. For continuous data the sample size, mean, standard deviation (SD), median, range (min, max) and interquartile range (Q1, Q3) will be presented. Categorical data will be displayed by absolute and relative frequencies (percentages). Percentages will be based on all non-missing values. Missing categories might be displayed in addition (only by absolute frequencies). Exceptions to this rule are

to be specified explicitly. In any case, the percent basis will be specified in a table footnote. Percentages will be rounded to one decimal place.

For hypothesis testing, statistical significance is controlled at the 1-sided, 0.025 alpha level and the shifted null hypothesis. Point estimators will be presented with 2-sided 95% confidence intervals.

For responder and change from baseline analyses planned to be conducted at a certain month of age/after treatment start (e.g. at 12m, 24m, 36m), the closest assessment within a time frame of ±2 months will be used for the analysis, unless otherwise specified. This time frame considers that visits take place every four months. If there was no assessment within this time frame, the value is assumed to be missing.

The index date for each patient will be the date of the therapy decision. If the therapy decision was not documented, the index date will be the date of the first treatment administration (of the treatment the patient was allocated to). The closest visit before or at the index date will be used as baseline visit. .

Every switch between the study medications risdiplam, nusinersen and onasemnogene abeparvovec (exception: initial therapy is documented for less than three months followed by an alternative therapy) will be considered a treatment switch, including switches between nusinersen and onasemnogene abeparvovec within the control arm.

4.1.1 Confounder

Confounders have been identified in advance through systematic research, as described in the Protocol Section 8.7.4. The following confounders will be considered.

Table 5: Confounders

Confounder	Type of variabel	Clinical relevance [a]	Definition	Operationalization in SMArtCARE eCRF	Applicable to analysis population
SMN2 copy number	Discrete	Very important	SMN2 copy number	Genetic Test Result: SMN2 copy number	All
Age at symptom onset	Continuous	Less important	Age of symptom onset in months for symptomatic patients	Clinical Diagnosis: Age at symptom onset	SMA type 1, SMA type 2, SMA type 3
Age at treatment initiation	Continuous	Very important	Age in weeks at treatment initiation	Registries, Clinical Trials: Age at visit AT	Pre-symptomatic patients: directly SMA type 1, SMA type 2, SMA type 3:

Confounder	Type of variabel	Clinical relevance [a]	Definition	Operationalization in SMArtCARE eCRF	Applicable to analysis population
				Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN(Date of treatment)	Derived (treatment delay defined as time from symptom onset to treatment initiation)
Early diagnosis	Discrete	Very important	Neonatal screening and early diagnosis	Baseline characteristics, newborn screening	All
Nutrition support	Discrete	Very important	Gastric tube or nasal feeding tube (exclusive/ supplemental/ no ne) at treatment initiation	Nutrition: Does the patient use a gastric or nasal feeding tube? AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN(Date of treatment)	SMA type 1, SMA type 2, SMA type 3
Ventilation support	Discrete	Very important	Duration of ventilator use (nighttime/intermittent/ permanent (≥16h/day) at treatment initiation	Pulmonary: Does the patient receive ventilator support? = Yes AND Pulmonary: Time of ventilator use 1. Night (during sleep) 2. Intermittent day time and continuous at night 3. Continuous (>16h/day) AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	SMA type 1, SMA type 2, SMA type 3

Confounder	Type of variabel	Clinical relevance [a]	Definition	Operationalization in SMArtCARE eCRF	Applicable to analysis population
Contractures	Discrete	Less important	Contractures limiting function (yes/no) at treatment initiation	Clinical Examination: Are any contractures present? = Yes AND Registries, Clinical Trials: Type of limitation = Severe (imposing limits to function) AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	SMA type 1, SMA type 2, SMA type 3
Motoric function: Highest motor milestone (at treatment initiation)	Discrete	Very important	Highest motor milestone at treatment initiation: None/n.a. Sitting without support Crawl on hands and knees Standing without support Walking without support Climb stairs	Best current motor function: Best current motor function AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	SMA type 2, SMA type 3
Motoric Function CHOP-INTEND	Discrete	Very important	CHOP-INTEND score at treatment initiation	CHOP-INTEND: Score AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	All
Motoric Function: HFMSE score	Discrete	Very important	Mean Hammersmith score treatment initiation	HFMSE: total AT	SMA type 1, SMA type 2 SMA type 3

Confounder	Type of variabel	Clinical relevance [a]	Definition	Operationalization in SMArtCARE eCRF	Applicable to analysis population
				Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	
Physical activity	Discrete	Less important	Physiotherapy		SMA type 1, SMA type 2
Multiple disorders	Discrete	Less important	Multiple disorders	Medical history	SMA type 1, SMA type 2, SMA type 3

All confounder variables will be included in the propensity score model as indicated by their type (continuous, discrete), as long as the criteria regarding the amount of missing data as specified below is fulfilled.

4.1.2 Propensity Score

To adjust for differences in the confounder variables between the treatment groups, propensity score weighting will be applied if sufficient overlap and balance between the scores is given, as detailed below.

The propensity score is the probability that a patient was assigned to a treatment conditional on the observed baseline covariates, $e(x) = \mathrm{pr}(z = 1 \mid x)$, and will be estimated using logistic regression (6).

After calculation of propensity scores for each patient, the overlap of propensity scores between the treatment groups will be evaluated. To date, there is no established criterion for sufficient overlap. Thus an overlap is considered sufficient if the overlap of propensity score distributions between the treatment groups is >50%, which is in accordance with the rules defined in the onasemnogene abeparvovec study protocol (7). If applicable guidelines are available at a later date, the criterion used might be amended. If the overlap is not sufficient for applying propensity score methods, only naïve comparisons will be performed.

In case of sufficient overlap, weights will be calculated based on the propensity scores. Two weighting methods will be considered, inverse probability of treatment weights (IPTW) and fine stratification weights (8). IPTW defines the weights for treated patients as $1/PS$ and weights for patients in the comparison arm as $1/(1-PS)$. To avoid extreme weights, propensity scores above 0.95 and below 0.05 will be excluded from the analysis. For fine stratification weights, the propensity scores are used to define fine stratums (9). A fixed width of 0.1 will be used to define stratums, resulting in 10 stratums total. Weights are then calculated based on the total number of patients within each stratum, for all stratums with at least one treated and one reference patient, and are defined as ($N_{\text{total in PS stratum i}}$ / N_{total}) / ($N_{\text{exposed in PS stratum i}}$ / $N_{\text{total exposed}}$) for treated patients, and as ($N_{\text{total in PS stratum i}}$ / N_{total}) / ($N_{\text{reference in PS stratum i}}$ / $N_{\text{total reference}}$) for the comparison.

For both weighting methods, the balance between treatment groups for each confounder variable will be evaluated by calculating standardized differences after weighting. The balance is sufficient for performing propensity score analyses if $abs(SMD) < 0.2$ is given for each confounder. Otherwise, only naïve comparisons are performed. If both weighting methods show sufficient balance between the treatment groups, the weighting method with the best overall confounder balance after weighting will be used for all analyses. As an overall measure of balance, the post-weighting C statistic can be used (10).

A detailed description of the unweighted and weighted analysis population will be done using baseline characteristics (as described in section 4.6.2).

4.1.3 Handling of Missing Data

For efficacy variables, an incomplete event date will be replaced by the last day of the month, assuming the month and year are known. For safety variables, an incomplete event date will be replaced by the first day of the month (assuming the month and year are known), unless there is evidence that the patient was event-free within that month, in which case the date the patient was last known to be event-free within that month will be used as the event date. Efforts to minimize the amount of missing dates are described in protocol section 8.6.1.

The Sponsor will emphasize to investigators the importance of collecting complete data, both for outcome measures and for the confounder variables at baseline required for the propensity score analysis described above.

In case missing data are still present in the confounder variables, the following steps will be performed.

4.1.3.1 Descriptive Analysis of Missing Data

The patterns of missing data for the confounder variables will be summarized with upset-plots by population and treatment group. Furthermore, the number of complete cases will be summarized.

Depending on the percentage of missing data the method to deal with it will be chosen, as described below.

4.1.3.2 Dealing with Missing Data

There are different methods to deal with missing data. For this study complete case analysis and multiple imputation are considered. It is planned to align with the rules of thumb described by Jakobsen et al. (11). According to these rules missing data can be ignored, if the proportion of missing data is below 5%. On the other hand, it is not recommended to use multiple imputation, if more than 40% of the data is missing. With multiple confounder variables there are two ways to assess the proportion of missing data, at subject level and at variable level. It is planned to focus on the subject level first. If 95% or more of the subjects have no missing confounder variables the complete case analysis will be used, meaning that only patients without missing confounder variables will be included in the analysis. Otherwise the percentages of subjects with missing data per confounder variable will be considered. All variables with an amount of missing data below 40% percent will be included in the multiple imputation approach (described below). Variables with more than 40% of subjects with missing data are not imputed at all and are not used as confounder. If a variable is excluded due to this rule, the distribution between the treatment arms will be assessed after the propensity weights are implemented. The resulting limitations due to potential imbalances will be described in the report.

4.1.3.3 Multiple Imputation

The confounder variables to be included in the multiple imputation are selected as described before. The missing variables will be imputed by non-missing baseline covariates using the multiple imputation by chained equations (MICE) algorithm (12). For numeric variables the Predictive mean matching method is used and for factorial variables the Logistic regression method (for 2 factors), the Multinomial logit model (for >2 factors) or the ordered logit model (for >2 ordered factors) is used.

1000 imputed datasets will be generated. For each dataset, propensity scores will be estimated using logistic regression, as described above. For each patient, propensity scores will be averaged across all imputed datasets, following the across-approach previously described (13–15) . Based on the averaged propensity scores, the overlap between treatment groups will be evaluated, weights will be generated if appropriate and the balance of confounder variables will be evaluated (Section 4.1.2). All statistical analyses described in Sections 4.2 - 4.5 will be conducted with the chosen weights.

4.2 PRIMARY ENDPOINT ANALYSIS

4.2.1 Definition of Primary Enpoints

Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene:

The primary endpoint is the number of AE leading to hospitalization over time. The primary estimand is defined as follows:

- Population: Presymptomatic patients with a 5q associated SMA and up to three copies of the *SMN2* gene as defined by the study inclusion and exclusion criteria (see Section 8.2.1 of the protocol)
- Endpoint: number of AE leading to hospitalization over time
- Treatment (see Section 8.2.2 of the protocol):
    - Experimental arm: Risdiplam according to SmPC
    - Control arm: Nusinersen or onasemnogene abeparvovec according to SmPC
- Intercurrent events and handling strategies:
    - Early discontinuation from study treatment: Treatment-policy strategy
    - Treatment switch: Treatment-policy strategy
- Population-level summary: Rate ratio

Symptomatic patients with a clinically diagnosed SMA type 1:

The primary endpoint is the time to death or permanent ventilation. The primary estimand is defined as follows:

- Population: Symptomatic patients with a clinically diagnosed SMA type 1 (see Section 8.2.1of the protocol)
- Endpoint: Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day)
- Treatment (see Section 8.2.2 of the protocol):
    - Experimental arm: Risdiplam according to SmPC
    - Control arm: Nusinersen or onasemnogene abeparvovec according to SmPC
- Intercurrent events and handling strategies:
    - Early discontinuation from study treatment: Treatment-policy strategy
    - Treatment switch: Treatment-policy strategy
- Population-level summary: hazard ratio

Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene:

The primary endpoint is the change from baseline of RULM total score at 12 months after treatment start. The primary estimand is defined as follows:

- Population: Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene (see Section 8.2.1 of the protocol). Only patients with a baseline value and a value at month 36 after treatment start are included.

- Endpoint: Change from baseline of RULM total score at 36 months after treatment start
- Treatment (see Section 8.2.2 of the protocol):
  - Experimental arm: Risdiplam according to SmPC
  - Control arm: Nusinersen or onasemnogene abeparvovec according to SmPC
- Intercurrent events and handling strategies:
  - Early discontinuation from study treatment: Treatment-policy strategy
  - Treatment switch: Treatment-policy strategy
- Population-level summary: Cohen's d

Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:

The primary endpoint is the change from baseline of RULM total score at 12 months after treatment start. The primary estimand is defined as follows:

- Population: Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene (see Section 8.2.1 of the protocol). Only patients with a baseline value and a value at month 36 after treatment start are included.
- Endpoint: Change from baseline of RULM total score at 36 months after treatment start
- Treatment (see Section 8.2.2 of the protocol):
  - Experimental arm: Risdiplam according to SmPC
  - Control arm: Nusinersen or onasemnogene abeparvovec according to SmPC
- Intercurrent events and handling strategies:
  - Early discontinuation from study treatment: Treatment-policy strategy
  - Treatment switch: Treatment-policy strategy
- Population-level summary: Cohen's d

Table 6: Operationalization of primary endpoints in SMArtCARE eCRF

Primary Endpoint	Fields of SMArtCARE eCRF
Pre-symptomatic patients Number of AE leading to hospitalization over time	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Adverse events: Date recorded • Adverse events: Has there been any adverse event since the last visit? • Adverse events: Has there been unplanned or prolonged hospitalisation? • Adverse events: Start date
Patients with SMA Type 1	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment)

Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day)	• End of data collection: Date of death • Medical assessment: Visit date • Medical assessment: Start of ventilator use • Medical assessment: Ongoing use of ventilator? • Medical assessment: End of ventilator use • Medical assessment: Time of ventilator use = Continuous (>16h/day)
Patients with SMA Type 2 Change from baseline of RULM total score at 36 months after treatment start	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • RULM: Date of assessment • RULM: Total RULM score
Patients with SMA Type 3 Change from baseline of RULM total score at 36 months after treatment start	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • RULM: Date of assessment • RULM: Total RULM score

4.2.2 Main Analytical Approach for Primary Endpoint(s)

Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the SMN2 gene:

The rationale of using FAS population and treatment policy strategy for the primary estimand is to provide a picture of a treatment effect foreseen in clinical practice when treatment (including treatment switches) is administered. Additional analysis applying hypothetical strategy to treatment switches (intercurrent events) will also be provided (details see Section 4.2.3).

The main analysis for the primary endpoint will be performed using a negative binomial regression model, which accounts for different follow-up times, with the patient's number of AE leading to hospitalization as a function of treatment arm and the time that each patient stays in the included as an offset in the model. This analytic model estimates the rate ratio, which quantifies the risk of AE leading to hospitalization associated with risdiplam in comparison to the control arm.

Symptomatic patients with a clinically diagnosed SMA type 1:

The rationale of using FAS population and treatment policy strategy for the primary estimand is to provide a picture of a treatment effect foreseen in clinical practice when treatment (including treatment switches) is administered. Additional analysis applying hypothetical strategy to treatment switches (intercurrent events) will also be provided (details see Section 4.2.3).

The primary efficacy variable is time to death or permanent ventilation, defined as the time from index date to the date death or the start date of permanent ventilation (whichever occurs first). Permanent ventilation is defined as two consecutive

documentations of permanent ventilation of more than 16 hours/day. Patients who have not had an event will be censored at the date they are last known to be alive and event free on or prior to the clinical cutoff date. Data for patients who are enrolled without any post baseline assessments will be censored at the date of index date plus 1 day.

The main analysis for the primary endpoint will be performed using a Cox proportional hazards model. A Cox-regression test will be performed and the hazard ratio (and 95% confidence interval (CI)) will be estimated.

Time to death or permanent ventilation will be presented graphically using Kaplan-Meier curves and with the median and 25% quantiles based on the Kaplan-Meier approach. Additionally, the p-value will be presented based on a 1-sided Logrank test.

Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the SMN2 gene:

The rationale of using FAS population and treatment policy strategy for the primary estimand is to provide a picture of a treatment effect foreseen in clinical practice when treatment (including treatment switches) is administered. Additional analysis applying hypothetical strategy to treatment switches (intercurrent events) will also be provided (details see Section 4.2.3).

The main analysis for the primary endpoint will be performed using a MMRM. The model will include the change from baseline at the visits up to 36 months as response variable and will include the categorical covariates of treatment group, visit, visit-by-treatment group interaction, baseline RULM Total Score (continuous), as fixed effects. The MMRM model will assume an unstructured covariance structure. If there are convergence problems with the model, then a heterogeneous compound symmetry or an autoregressive (AR) (1) covariance structure may be fitted.

With the estimated means and standard deviations, Cohen's d will be estimated as a measure of the effect size via $d = \frac{M_1 - M_2}{SD_{pooled}}$. The estimated treatment difference in the mean change from baseline will be presented with a 95% CI and the p-value will be presented based on a 1-sided t-test. The score and change from baseline score will also be summarized using descriptive statistics. The mean absolute scores and change from baseline scores over time will also be presented graphically using a line plot.

As part of the regular SMArtCARE guidelines for follow-up monitoring the RULM is used for follow-up monitoring of the following patients: Children > 2 years and adults: For all patients with ability to sit in a wheelchair. Only patients fulfilling the criteria for using the RULM at baseline with a baseline value and a value at month 36 after treatment start will be included in the analysis.

Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:

As described above for type 2 patients.

4.2.3 Supplementary Analyses

Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene:

The analysis method, population, and definition of intercurrent events will be the same as the main analysis (Section 4.2.1). However, all treatment switches will follow a hypothetical strategy, where for patients that switch treatments (risdiplam, nusinersen, onasemnogene abeparvovec) only AE leading to hospitalization before the treatment switch will be included in the analysis. The follow up times included into the negative binominal regression model for these patients ends with the treatment switch.

Symptomatic patients with a clinically diagnosed SMA type 1:

The analysis method, population, and definition of intercurrent events will be the same as the main analysis (Section 4.2.1).

However, all treatment switches will follow a hypothetical strategy, where the time to death or permanent ventilation will be censored at the date of treatment switch, to estimate a treatment effect in the absence of treatment switches.

Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the SMN2 gene:

The analysis method, population, and definition of intercurrent events will be the same as the main analysis (Section 4.2.1). However, all treatment switches will follow a hypothetical strategy, where all values will be censored after the occurrence of the intercurrent event, to estimate a treatment effect in the absence of treatment switches. Data censored after treatment switches following hypothetical strategy will be implicitly imputed by the MMRM model assuming missing at random (MAR).

Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the SMN2 gene:

As described above for type 2 patients.

4.2.4 Sensitivity Analyses

To analyze the heterogenity in the control arm which includes both patients treated with nusinersen and patients treated with onasemnogene abeparvovec, sensitivity analyses will be performed. The primary endpoints for all populations will be analyzed by comparing patients in the experimental arm treated with risdiplam separately to patients

treated with nusinersen, as well as patients treated with onasemnogene abeparvovec. The analysis method, population, and definition of intercurrent events will be the same as the main analysis.

As an additional sensitivity analysis, the primary analysis will also be conducted on the patient population with prospective enrollment to assess the adequacy of a pooled analysis for retrospective and prospective enrolled patients.

4.3 SECONDARY ENDPOINTS ANALYSES

Time to event analyses will be presented graphically using Kaplan-Meier curves. The median time and the 25% quantile (and 95% CIs) will be presented. To quantify the treatment effect, the hazard ratio (and 95% 2-sided CI) will be estimated using a Cox proportional hazards model, p-values will be presented based on a 1-sided Cox Regression test. Additionally, p-values will be presented based on a 1-sided Logrank test.

Responder analyses will describe the number and percentage of patients who are classified as a responder. To compare between treatment arms, relative and absolute effect measures will be presented, including absolute risk reduction, odds ratio and relative risk with corresponding 95% CIs. Calculation of these effect measures will be model-based using a logistic regression model. Wald p-values (1-sided) will be presented for the relative risk.

For analyses describing the change from baseline, an MMRM analysis will be performed as described in Section 4.2.2. With the estimated means and standard deviations, Cohen's d will be estimated as a measure of the effect size via $d = \frac{M_1 - M_2}{SD_{pooled}}$. The estimated treatment difference in the mean change from baseline will be presented with a 95% CI and the p-value will be presented based on a 1-sided t-test. The values and change from baseline values will also be summarized using descriptive statistics. The mean absolute values and change from baseline values over time will be presented graphically using a line plot.

4.3.1 Secondary Endpoints

Table 7: Operationalization of secondary endpoints in SMArtCARE eCRF

Variable	Fields of SMArtCARE eCRF
Secondary Variables (as applicable)	
Time to death	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN (Date of treatment) • End of data collection: Date of death
Time to permanent ventilation (two consecutive documentations of permanent ventilation of >16 hours/day)	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Start of ventilator use • Medical assessment: Ongoing use of ventilator?

	• Medical assessment: End of ventilator use • Medical assessment: Time of ventilator use = Continuous (>16h/day)
Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day)	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • End of data collection: Date of death • Medical assessment: Visit date • Medical assessment: Start of ventilator use • Medical assessment: Ongoing use of ventilator? • Medical assessment: End of ventilator use • Medical assessment: Time of ventilator use = Continuous (>16h/day)
Time to any respiratory support	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Does the patient receive ventilator support? • Medical assessment: Type of ventilation o Non-invasive o Invasive
Time from first treatment to reaching the WHO motor development milestone “sitting without support”	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Best current motor function = Sitting or higher current motor function • Medical assessment: Age gained of new motor milestone • Medical assessment: Age at visit (if age gained of new motor milestone not filled)
Time from first treatment to reaching the WHO motor development milestone “standing without support”	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Best current motor function = Standing without support or higher current motor function • Medical assessment: Age gained of new motor milestone • Medical assessment: Age at visit (if age gained of new motor milestone not filled)
Time from first treatment to reaching the WHO motor development milestone “walking without support”	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Best current motor function = Walking without support • Medical assessment: Age gained of new motor milestone Medical assessment: Age at visit (if age gained of new motor milestone not filled)
Time from gaining WHO motor development milestone to permanent loss of milestone ability: • Loss of the ability to sit without support • Loss of the ability to stand without support • Loss of the ability to walk without support	• Medical assessment: Best current motor function • Medical assessment: Changes in motor milestones • Medical assessment: Age gained of new motor milestone • Medical assessment: Age loss of previous motor milestone • Medical assessment: Age at visit (if age gained/loss of motor milestone not filled)
Change from baseline in CHOP INTEND total score	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment)

at 12, 24 and 36 months after treatment start	• CHOP-INTEND: Date of evaluation CHOP-INTEND: Score
Change from baseline in HFMSE total score at 12, 24 and 36 months after treatment start	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • HFMSE: Date of assessment • HFMSE: Extended Total HFMSE
Change from baseline in RULM total score at 12 and 24 months after treatment start	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • RULM: Date of assessment • RULM: Total RULM score
For ambulatory patients: relative change from baseline in walking distance at 12, 24 and 36 months after treatment start	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Walk test: Date of assessment • Walk test: distance_na
For ambulatory patients: Evaluation of the total walking distance at month 36 after treatment start	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Walk test: Date of assessment • Walk test: distance_na
Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after treatment start	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Swallowing? = With difficulties • Medical assessment: Does the patient use a gastric or nasal feeding tube? = Yes - exclusively fed by tube • Medical assessment: Does the patient use a gastric or nasal feeding tube? = Yes – supplementary e.g. for fluids. • Medical assessment: Start of tube feeding (date) • Medical assessment: Visit date (if start of feeding tube not filled).
Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after treatment start	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Does the patient use a gastric or nasal feeding tube? = Yes - exclusively fed by tube • Medical assessment: Does the patient use a gastric or nasal feeding tube? = Yes – supplementary e.g. for fluids • Medical assessment: Start of tube feeding (date) • Medical assessment: Visit date (if start date of feeding tube not filled)
Proportion of patients with age-appropriate Bayley III scores in the subscales “Expressive Language” and “Receptive Language” at 24 months of age	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Bayley: Date of Evaluation • Bayley: Expressive Language • Bayley: Receptive Language
Time to first documentation of scoliosis or orthopedic surgery	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Does the patient have scoliosis? • Medical assessment: Orthopedic surgery since last visit?

Time to first documentation of scoliosis	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Does the patient have scoliosis?
Time to first documentation of orthopedic surgery	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Orthopedic surgery since last visit?
Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Planned hospitalization since last visit (except for treatment administration)? • Medical assessment: Admission date • Nusinersen/onasemnogene abeparvovec; Care setting = Inpatient (overnight)? Note: Onasemnogene abeparvovec is exclusively administered in an inpatient setting in Germany. SMArtCARE CRF accordingly refers to the hospitalization for treatment. One planned hospitalization is counted for each patient receiving onasemnogene abeparvovec at the date of treatment.

4.3.1.1 Time to death

Time-to-death is defined as the time in months from the date of first treatment administration until the date of death from any cause. Patients with no death reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be alive. Patients who have been withdrawn from the study with no event reported prior to withdrawal will be censored at the date of withdrawal.

4.3.1.2 Time to permanent ventilation

Time to permanent ventilation is defined as the time from date of first treatment administration to the first documentation of permanent ventilation. Permanent ventilation is defined as two consecutive documentations of ventilation of at least 16 hours per day. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be without permanent ventilation. Patients who have been withdrawn from the study with no event reported prior to withdrawal will be censored at the date of withdrawal.

4.3.1.3 Time to death or permanent ventilation

See Section 4.2.1.

4.3.1.4 Time to any respiratory support

Time to any respiratory support is defined as the time from date of first treatment administration to the first documentation of ventilator support. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the

cutoff in which they were known to be without any respiratory support. Patients who have been withdrawn from the study with no event reported prior to withdrawal will be censored at the date of withdrawal.

4.3.1.5 Time from first treatment to reaching the WHO motor development milestone “sitting without support”

Time to reaching the WHO motor development milestone “sitting without support” is defined as the time from date of first treatment administration to the first documentation of reaching the WHO motor development milestone “sitting without support”. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to have not reached the motor milestone. Patients who have been withdrawn from the study with no event reported prior to withdrawal will be censored at the date of withdrawal. Patients who have reached the motor milestone “sitting without support” at the time of first treatment administration will be excluded from the analysis.

4.3.1.6 Time from first treatment to reaching the WHO motor development milestone “standing without support”

Time to reaching the WHO motor development milestone “standing without support” is defined as the time from date of first treatment administration to the first documentation of reaching the WHO motor development milestone “standing without support”. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to have not reached the motor milestone. Patients who have been withdrawn from the study with no event reported prior to withdrawal will be censored at the date of withdrawal. Patients who have reached the motor milestone “standing without support” at the time of first treatment administration will be excluded from the analysis.

4.3.1.7 Time from first treatment to reaching the WHO motor development milestone “walking without support”

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Time to reaching the WHO motor development milestone “walking without support” is defined as the time from date of first treatment administration to the first documentation of reaching the WHO motor development milestone “walking without support”. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to have not reached the motor milestone. Patients who have been withdrawn from the study with no event reported prior to withdrawal will be censored at the date of withdrawal. Patients who have reached the motor milestone “walking without support” at the time of first treatment administration will be excluded from the analysis.

4.3.1.8 Time from gaining WHO motor development milestone to permanent loss of milestone ability: Loss of the ability to sit without support

Time to the permanent loss of the ability to sit without support is defined as the time from the date of gaining the WHO motor development milestone “sitting without support” to the first documentation of loss of the milestone ability. Documentation of the new (worsened) highest motor milestone at 2 consecutive visits is required. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to have not lost the motor milestone. Patients who have been withdrawn from the study with no event reported prior to withdrawal will be censored at the date of withdrawal.

Only patients who have a documented date for gaining the motor milestone “sitting without support” will be included in the analysis.

4.3.1.9 Time from gaining WHO motor development milestone to permanent loss of milestone ability: Loss of the ability to stand without support

Time to the permanent loss of the ability to stand without support is defined as the time from the date of gaining the WHO motor development milestone “standing without support” to the first documentation of loss of the milestone ability. Documentation of the new (worsened) highest motor milestone at 2 consecutive visits is required. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to have not lost the motor milestone. Patients who have been withdrawn from the study with no event reported prior to withdrawal will be censored at the date of withdrawal.

Only patients who have a documented date for gaining the motor milestone “standing without support” will be included in the analysis.

4.3.1.10 Time from gaining WHO motor development milestone to permanent loss of milestone ability: Loss of the ability to walk without support

Time to the permanent loss of the ability to walk without support is defined as the time from the date of gaining the WHO motor development milestone “walking without support” to the first documentation of loss of the milestone ability. Documentation of the new (worsened) highest motor milestone at 2 consecutive visits is required. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to have not lost the motor milestone. Patients who have been withdrawn from the study with no event reported prior to withdrawal will be censored at the date of withdrawal.

Only patients who have a documented date for gaining the motor milestone “walking without support” will be included in the analysis.

4.3.1.11 Change from baseline in CHOP INTEND total score at 12, 24 and 36 months after treatment start

The change from baseline in the CHOP INTEND total score at 12, 24 and 36 months after treatment start will be presented.

The CHOP-INTEND consists of 16 items scored from 0 to 4, with a higher score indicating better motor skills. Both the left and right sides are scored and the maximum score is selected for the final item score. The total score is calculated by summing the item scores to give a maximum possible score of 64. If an individual item is missing or 'Cannot Test (CNT)' is recorded, the item score will be set to 0.

As part of the regular SMArtCARE guidelines for follow-up monitoring, the CHOP-INTEND is used for the following patients: Children: All children < 2 years of age; All patients > 2 years of age without ability to sit. Adults: For patients without ability to sit.

Only patients fulfilling the criteria for using the CHOP-INTEND at baseline with a baseline value and a value at the respective month after treatment start will be included in the analysis.

4.3.1.12 Change from baseline in HFMSE total score at 12, 24 and 36 months after treatment start

The change from baseline in the total score of HFMSE at 12, 24 and 36 months after treatment start will be presented.

The HFMSE was developed to assess the motor function ability of individuals aged two years or older, with Type 2 and 3 SMA (16). The scale contains 33 items which score on a 3-point Likert scale (0-2) and are summed to derive the total score, with lower scores indicating greater impairment. The HFMSE was designed to assess important functional abilities, including standing, transfer, ambulation, and proximal and axial function.

For items recorded as "Not Done" for the HFMSE scale, these items are considered as missing with missing item scores.

If 6 or fewer items are missing, the missing items will be imputed to be "0" (unable to perform the task) prior to the calculation of the total score of HFMSE. If more than 6 items are missing at an assessment time point, the total score of HFMSE at this assessment time point will not be calculated.

As part of the regular SMArtCARE guidelines the HFMSE I is used for follow-up monitoring of the following patients: Children > 2 years for all patients with ability to sit; If CHOP INTEND score >50: CHOP INTEND and HFMSE; If CHOP INTEND score >60: HFMSE instead of CHOP INTEND. Adults: All patients with ability to sit.

Only patients fulfilling the criteria for using the HFMSE at baseline with a baseline value and a value at the respective month after treatment start will be included in the analysis.

4.3.1.13 For ambulatory patients: relative change in walking distance from baseline at 12, 24 and 36 months after treatment start

For the relative change from baseline in walking distance at months 12, 24 and 36 after treatment start, the mean relative distance and relative change from baseline distance at each time point will be summarized using descriptive statistics and presented graphically using a line plot.

Walking distance describes the distance walked in the 6 minute walking test.

As part of the regular SMArtCARE guidelines for follow-up monitoring, the test is used for the following patients: > 2 years for all patients with ability to walk.

Only patients fulfilling the criteria for using the 6 minute walking test at baseline with a baseline value and a value at the respective month after treatment start will be included in the analysis.

4.3.1.14 For ambulatory patients: evaluation of the total walking distance at month 36 after treatment start

For the evaluation of the total walking distance at month 36 after treatment start, the mean total distance and difference between means will be summarized using descriptive statistics.

4.3.1.15 Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after treatment start

The assessed swallowing function is ordered as follows:

1. No feeding tube, swallowing = normal
2. No feeding tube, swallowing = with difficulties
3. Feeding tube (supplementary e.g. for fluids)
4. Feeding tube (exclusively fed by tube)

A shift table will present the number/percentage of patients per category at 12, 24 and 36 months after treatment start versus the corresponding swallowing function at baseline.

4.3.1.16 Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after treatment start

Non-oral nutritional support includes the use of a gastral or nasal feeding tube, either exclusively or supplementary.

The proportion of patients with need of non-oral nutritional support at 12, 24 and 36 months after treatment start will be presented. Patients who have needed non-oral nutritional support at least once between the start of treatment and the respective time point will be classified as responders. Patients who have no need of non-oral nutritional support, or have been withdrawn, or died, will be classified as non-responders for the

analysis. Patients with only missing assessments will also be classified as non-responders.

4.3.1.17 Proportion of patients with age-appropriate Bayley III scores in the subscales "Expressive Language" and "Receptive Language" at 24 months of age

The proportion of patients with age-appropriate Bayley III scores in the subscales "Expressive Language" and "Receptive Language" at 24 months of age will be presented. Patients who do not show age-appropriate Bayley III scores will be classified as non-responders for the analysis. Patients with a missing Bayley III score assessment at month 24 will also be classified as non-responders, if the patient was in the study at this age and the option for an age-appropriate Bayley III assessment was given.

The Bayley scale of infant development (BSID)-III assesses the developmental progress of infants and young children, and is primarily used to identify children with developmental delays and to evaluate the impact of intervention efforts. The BSID-III consists of a core battery of five scales: three scales are administered with child interaction, the Cognitive Scale, the Language Scale (Receptive Communication and Expressive Communication), and the Motor Scale (Fine Motor and Gross Motor); two additional scales (Social-Emotional and Adaptive Behavior) are conducted with parent/caregiver questionnaires (Bayley 2006).

Age-appropriate scores will be defined as growth scores above the 5th percentile at month 24 as given in the BSID-III manual.

As part of the regular SMArtCARE guidelines for follow-up monitoring, the Bayley III is evaluated once for children at the age of 24 months. Only patients with the option for an age-appropriate Bayley III assessment at month 24 of age are included in the analysis.

4.3.1.18 Time to first documentation of scoliosis or orthopedic surgery

Time to first documentation of severe scoliosis or orthopedic surgery is defined as the time from date of first treatment administration to the first documentation of scoliosis or to the first documentation of orthopedic surgery, whichever comes first. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be without scoliosis or orthopedic surgery. Patients who have been withdrawn from the study with no event reported prior to withdrawal will be censored at the date of withdrawal. Patients with scoliosis at the time of treatment start will be excluded from the analysis.

4.3.1.19 Time to first documentation of scoliosis

Time to first documentation of scoliosis is defined as the time from date of first treatment administration to the first documentation of scoliosis. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be without scoliosis. Patients who have been withdrawn from the study with no event reported prior to withdrawal will be censored at the date of

withdrawal. Patients with scoliosis at the time of treatment start will be excluded from the analysis.

4.3.1.20 Time to first documentation of orthopedic surgery

Time to first documentation of orthopedic surgery is defined as the time from date of first treatment administration to the first documentation of orthopedic surgery. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be without any orthopedic surgery. Patients who have been withdrawn from the study with no event reported prior to withdrawal will be censored at the date of withdrawal. Patients with severe scoliosis at the time of treatment start will be excluded from the analysis.

4.3.1.21 Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)

The comparison of the number of planned hospitalization over time between the arms will be performed using a negative binomial regression model, which accounts for different follow-up times, with the patient's number of planned hospitalizations as a function of the treatment arm and the time that each patient stays in the hospital included as an offset in the model. This analytic model estimates the rate ratio, which quantifies the risk of planned hospitalization associated with risdiplam in comparison to the control arm.

4.4 SUBGROUP ANALYSES

Subgroup analyses will be performed to investigate the generalizability of the results when comparing risdiplam to the control arm.Analyses will be presented for the following subgroups:

Table 8: Subgroups

Subgroups	Categories	Populations
Sex	Male, female	All
Age at treatment initiation	0 to 18 months, 18 months to 5 years, 6 to 11 years, 12 to 17 years, and 18 to 25 years, > 25 years	All
Geographic region	Germany, Austria	All
History of scoliosis surgery	Yes, no	SMA2, SMA3
Highest motor milestone at baseline (disease severity)	None, Sitting without support, Crawl on hands and knees, Standing without support, Walking without support, Climb stairs	All
Nutrition support	Yes – exclusively, yes – supplementary, no	All

Subgroups	Categories	Populations
Ventilation support	Yes, no	All
Contractures	Yes, no	SMA1, SMA2, SMA3
SMN2 Copy Number	1, 2, 3	All
Baseline CHOP-INTEND	⩽ median score, > median score[a]	SMA1, presymptomatic
Baseline HFMSE score	⩽ median score, > median score	SMA2, SMA3
Baseline CMAP amplitude	<1.5mV, ⩾1.5mV	presymptomatic
Time between first treatment and onset of symptoms	⩽ 3 months, > 3 months	SMA1

[a] in accordance with the real world data collection for the reassessment of the additional benefit of onasemnogene abeparvovec

Interaction tests (likelihood-ratio-tests) will be done for all subgroups, excluding categories like “missing” or “unknown”. The corresponding p-values will not be interpreted if in both arms combined there are less than 10 patients or events in one category. The significant interactions will be discussed in detail in the report. The consistency of the results across the various endpoints will be assessed, as well as the concordance of the effects in the individual subgroup categories. During the interpretation of the results it will also considered whether there is a medical rationale for an effect modification.

4.5 SAFETY ANALYSES

4.5.1 Adverse Events

Table 9: Operationalization of safety endpoints in SMArtCARE eCRF

Variable	Fields of SMArtCARE eCRF
Safety Variables	
Number of AE leading to hospitalization over time	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Adverse events: Date recorded • Adverse events: Has there been any adverse event since the last visit? • Adverse events: Has there been unplanned or prolonged hospitalization? • Adverse events: Start date
Proportion of patients with a SAE	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Adverse events: Date recorded • Adverse events: Has there been any adverse event since the last visit? • Adverse events: Has there been unplanned or prolonged hospitalization? • Adverse event: Start date • Adverse event: Description of adverse event

Variable	Fields of SMArtCARE eCRF
Safety Variables	
Proportion of patients with an AE leading to hospitalization	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Adverse events: Date recorded • Adverse events: Has there been any adverse event since the last visit? • Adverse events: Has there been unplanned or prolonged hospitalization? • Adverse event: Start date
Proportion of patients with a selected SAE (each of the of the following): • retinopathy • effect on epithelial tissue • thrombocytopenia • nephropathy • hydrocephalus • hepatopathy • cardiac events • sensory neuropathy	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Adverse events: Date recorded • Adverse events: Has there been any adverse event since the last visit? • Adverse events: Has there been unplanned or prolonged hospitalization? • Adverse events: Any unexpected events without hospitalization? • Adverse events: Type of unexpected event • Adverse events: Start date • Adverse event: Description of adverse event

The analysis of safety outcomes/variables is based on SAE, AE leading to hospitalization and selected SAE. The number and percentage of patients with a (serious) adverse event in each category will be summarized and compared using relative and absolute effect measures, including absolute risk reduction, odds ratio and relative risk. Calculation of these effect measures will be model-based using a logistic regression model. Wald p-values (1-sided) will be presented for the relative risk.

All SAE, AE leading to hospitalization and selected SAE term entered by the physician describing the event (the “verbatim term”) will be assigned to a standardized term (the “preferred term”) based on the most up-to-date version of MedDRA. Data displays of SAE and selected SAE will be performed using the preferred terms and their according system organ class.

The proportion of patients with SAE, AE leading to hospitalization and selected SAE will be summarized using the preferred terms and their according system organ class.

The number of AE leading to hospitalization over time will be analyzed separately using negative binomial regression models.

All safety analyses will follow the hypothetical strategy for treatment switches. For responder analyses, only adverse events before the treatment switch will be considered. For the number of AE leading to hospitalization over time, only AE leading to hospitalization before the treatment switch will be included and the follow up times included into the negative binominal regression model for these patients end with the treatment switch. Additionally, all safety analyses will be analyzed using the treatment-policy strategy for all intercurrent events.

4.6 OTHER ANALYSES

4.6.1 Patient Disposition

All summaries will be done by treatment group and by retrospective / prospective enrolled patients.

Population details will be presented based on the total population in terms of:

- Number of patients enrolled (= FAS)
- Number of patients treated

The disposition will be summarized as the overall count and percentage of patients who completed respectively discontinued the study prematurely including the categories for the primary reason for withdrawal as specified in the CRF.

4.6.2 Summaries of Demographics and Baseline Characteristics

Demographic and baseline characteristics such as age, sex, geographic region, and baseline disease characteristics (such as history of scoliosis surgery, highest motor milestone, HFMSE score, nutrition support, ventilation support, contractures, SMN2 Copy Number, CHOP-INTEND, CMAP amplitude, time between first treatment and onset of symptoms, pre-existing illness, need for wheelchair, participation in other registries) will be summarized by treatment group and by retrospective / prospective enrolled patients using means, SDs, medians, and ranges for continuous variables, and counts and proportions for categorical variables, as appropriate.

4.6.3 Concomitant medication/ Therapy interventions

Concomitant medication on regular basis (treatment names), Therapy interventions (Physiotherapy, Feeding/Speech therapy, Occupational therapy, Other) and will be summarized by treatment group.

4.6.4 Extent of Exposure

The exposure (duration of treatment) to SMA-Medication (risdiplam, nusinersen,) will be summarized by treatment group. Dose and number of interruptions (> 4 weeks) for risdiplam will be summarized. The number of subjects treated with onasemnogene abeparvovec will be summarized.

The number of subjects that switched treatment will be summarized by treatment group. The exposure (duration of treatment) for the switched treatments will be summarized as well.

4.6.5 Orthoses/Devices/Wheelchair use

The use, location and type of orthoses, the use and type of devices and the use and type of wheelchairs will be summarized by treatment group and visit.

4.6.6 Observation period

The patient-related observation period will be summarized (median, min, max) by treatment group and by retrospective / prospective enrolled patients (overall and end-point specific if applicable).

4.7 INTERIM ANALYSES / STATUS REPORTS

4.7.1 Planned interim analyses and status reports

First status report (submission 6 months after study start):

Disposition, summaries of demographics / baseline characteristics, exposure and patient-related observation period will be analyzed as described above and will be presented in the status report. Further analyses might be conducted and presented if appropriate. The data cut for this analysis will be at study start (retrospective enrolled patients and, if possible, prospective enrolled patients).

Second status report and first interim analysis (submission 18 months after study start):

Disposition, summaries of demographics / baseline characteristics, exposure and patient-related observation period will be analyzed as described above. The primary endpoints (and secondary endpoints if appropriate) will be analyzed as described above. Module 4 of the dossier template will be used to submit the results. Based on this interim analysis, the sample size will be calculated using observed effect sizes and recruitment rates as assumptions considering all relevant endpoints.. If the expected power is less than 60% for a primary endpoint (and relevant secondary endpoints) the enrollment might be stopped due to futility in the respective population. For populations without a calculated sample size at study start, the same procedure will be conducted to check for futility. The data cut for this analysis will be 12 months after study start.

Third status report and second interim analysis (submission 30 months after study start):

Disposition, summaries of demographics / baseline characteristics, exposure and patient-related observation period will be analyzed as described above. The primary endpoints (and secondary endpoints if appropriate) will be analyzed as described above. Module 4 of the dossier template will be used to submit the results. If the expected power is less than 60% for a primary endpoint (and relevant secondary endpoints) the

enrollment might be stopped due to futility in the respective population. The data cut for this analysis will be 24 months after study start.

4.8 CHANGES TO PROTOCOL-PLANNED ANALYSES

Not applicable.

5. SUPPORTING DOCUMENTATION

This section is not applicable, since there is no additional supporting document.

6. REFERENCES

1. Dr. Astrid Pechmann. Longitudinal Data Collection from Patients with Spinal Muscular Atrophy: The SMArtCARE Database: Study protocol v2.1, 2022.
2. Finkel Richard S., Mercuri Eugenio, Darras Basil T., Connolly Anne M., Kuntz Nancy L., Kirschner Janbernd et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. doi: 10.1056/NEJMoa1702752.
3. Day JW, Finkel RS, Chiriboga CA, Connolly AM, Crawford TO, Darras BT et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of SMN2 (STR1VE): an open-label, single-arm, multicentre, phase 3 trial. Lancet Neurol; 20(4):284–93, 2021. doi: 10.1016/S1474-4422(21)00001-6.
4. Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. N Engl J Med; 378(7):625–35, 2018. doi: 10.1056/NEJMoa1710504.
5. Cohen J. Statistical Power Analysis for the Behavioral Sciences, 1988.
6. Paul Rosenbaum. The central role of the propensity score in observational studies for causal effects, 1983.
7. Novartis. Onasemnogen-Abeparvovec_AbD: Studienprotokoll; 2021.
8. Rishi J Desai,1 Jessica M Franklin1. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners, 2019.
9. Rishi J. Desai,a Kenneth J. Rothman,b,c Brian.T Bateman,a,d Sonia Hernandez-Diaz,e and Krista F. Huybrechtsa. A Propensity-score-based Fine Stratification Approach for Confounding Adjustment When Exposure Is Infrequent, 2017.
10. Franklin JM, Rassen JA, Ackermann D, Bartels DB, Schneeweiss S. Metrics for covariate balance in cohort studies of causal effects. Stat Med; 33(10):1685–99, 2014. doi: 10.1002/sim.6058.
11. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials - a practical guide with flowcharts. BMC Med Res Methodol; 17(1):162, 2017. doi: 10.1186/s12874-017-0442-1.

12. Stef van Buuren, Karin Groothuis-Oudshoorn. mice: Multivariate Imputation by Chained Equations in R, 2011.
13. Jennifer Hill. REDUCING BIAS IN TREATMENT EFFECT ESTIMATION IN OBSERVATIONAL STUDIES SUFFERING FROM MISSING DATA, 2004.
14. Robin Mitra and Jerome P Reiter. A comparison of two methods of estimating propensity scores after multiple imputation, 2016.
15. Walter L. Leite, Burak Aydin, and Dee D. Cetin-Berber. Imputation of Missing Covariate Data Prior to Propensity Score Analysis: A Tutorial and Evaluation of the Robustness of Practical Approaches, 2021.
16. Jessica M. O'Hagen, Allan M. Glanzman, Michael P. McDermott, Patricia A. Ryan, Jean Flickinger, Janet Quigley, Susan Riley, Erica Sanborn, Carrie Irvine, William B. Martens, Christine Annis, Rabi Tawil, Maryam Oskoui, Basil T. Darras, Richard S. Finkel, Darryl C. De Vivo. An expanded version of the Hammersmith Functional Motor Scale for SMA II and III patients, 2007.

Final Report

Systematic identification and validation of potential confounders

Patients with an indication of Spinal Muscular Atrophy (SMA)

Version 0.1
Date: 07-06-2024

Prepared for: [redacted]

Contact:
[redacted]

Content

Tables

Figures

Table 1: Index of abbreviations

Abbreviation	Definition
ADL	Activities of Daily Living
AWMF	Working Group of the Scientific Medical Societies e.V. (Arbeits gemeinschaft der Wissenschaftlichen Medizinischen Fachge sellschaften e.V.)
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CMA	Canadian Medical Association
CPG	Clinial Practice Guidelines
FVC	Forced Vital Capacity
HFMSE	Hammersmith Functional Motor Scale Expanded
HINE	Hammersmith Infant Neurological Exam
HTA	Health Technology Assessment
IQWiG	Institute for Quality and Efficiency in Health Care
KOL	Key Opinion Leader
RULM	Revised Upper Limb Module
SLR	Systematic Literature Review
SMA	Spinal Muscular Atrophy
SMN	Survival Motor Neuron
Treat-NMD	Translational Research in Europe for the Assessment and Treatment of Neuromuscular Disease
TRIP	Turning Research Into Practice
WHO	World Health Organization
6MWT	6-Minute Walk Test

1. Introduction and objective

Spinal muscular atrophy (SMA) is a rare, genetic neuromuscular disorder characterized by the progressive and irreversible loss of motor neurons, resulting in muscle wasting. This leads to advancing muscle weakness and paralysis, difficulties in swallowing and breathing, and, in more severe cases, premature death (Mercuri et al., 2018), (Kolb & Kissel, 2015).

SMA is caused by the homozygous deletion of the survival motor neuron gene 1 (*SMN1*), which results in a deficiency of survival motor neuron (SMN) protein (Kolb & Kissel, 2015). This protein is crucial for motor neuron health and survival. Additionally, there is a backup gene, survival motor neuron 2 (*SMN2*), which is closely homologous to *SMN1* and capable of producing the SMN protein. Individuals affected by SMA primarily rely on the *SMN2* gene due to a mutation on chromosome 5q that renders the *SMN1* gene unable to produce adequate levels of functional SMN protein. Nevertheless, it is important to note that only about 10–15% of the protein produced by *SMN2* is full-length and functional (Lefebvre et al., 1995), (Darbar et al., 2011). Research indicates that enhancing SMN protein levels offers significant clinical benefits for individuals across various SMA types (Anderton & Mastaglia, 2015).

SMA is classified into five types (0 through 4), each defined by symptom severity, age at onset, and motor milestones achieved. SMA type 0, detected prenatally, involves no motor milestones. Type 1 appears from 0 to 6 months, and is characterized by minimal head control and supported sitting. Type 2 occurs between 6 to 18 months, with the ability to sit but not stand independently. Type 3, emerging after 18 months, enables walking, while type 4, presenting in adulthood, maintains full motor functions (Angilletta et al., 2023). The number of *SMN2* gene copies an individual has is inversely related to the severity of the disease and correlates with the type of SMA; SMA type 0, the most severe form, is associated with only one copy of the *SMN2* gene. SMA type 1 patients have two copies, and SMA type 2 varies between two to three copies, indicating a moderate form of the disease; 97% of infants with two copies of *SMN2* will develop type 1 SMA. Conversely, infants with three *SMN2* copies have a 7% chance of developing type 1 SMA and an 83% chance of developing type 2 SMA. SMA type 3 patients possess three to four copies, leading to a milder disease manifestation. Lastly, SMA type 4, which presents in adulthood with the mildest symptoms, is characterized by the presence of four or more *SMN2* gene copies (Angilletta et al., 2023), (Calucho et al., 2018), (Wirth et al., 2020).

Infants with SMA type 1, while alert and aware, experience a loss of the ability to swallow and feed safely by mouth, and do not achieve any developmental milestones beyond their initial presentation. These infants develop progressive skeletal muscle weakness and atrophy, and they suffer from chronic ventilatory failure(Kolb & Kissel, 2015),(De Sanctis et al., 2018), (Wadman et al., 2020). SMA type 2 is characterized by the peak motor skill of being able to sit unsupported, typically reached around an average age of 1 year (Lin et al., 2015), (Farrar et al., 2017). In contrast, SMA type 3 is differentiated from type 2 by the ability of individuals to walk independently (Fujak et al., 2013).

The primary cause of mortality among these patients is respiratory failure (Mercuri et al., 2018), (Farrar et al., 2023). Infants with SMA experience rapid and significant muscle weakening, which progresses to the inability to breathe or swallow. Death typically occurs following a severe respiratory illness (Finkel et al., 2018). SMA type 0 typically has a life expectancy of less than 6 months. SMA type 1, also severe, has a life expectancy of less than 2 years, while patients with SMA type 2 generally have a life expectancy of more than 2 years. Both SMA types 3 and 4, which are less severe, allow individuals to reach adulthood with a reduced impact on life expectancy compared to the more severe types (Angilletta et al., 2023), (M. J. Wang et al., 2022).

The Institute for Quality and Efficiency in Health Care (IQWiG) issued a rapid report on May 13, 2020, titled "Concepts for the generation of data in health care settings and their evaluation for the purpose of assessing the benefit of drugs according to § 35a SGB V," version 1.1 (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2020). This document offers guidance on how to analyze patient-specific data within the context of drug benefit assessments under § 35a SGB V. IQWiG addresses crucial elements such as the planning of studies and statistical analyses, as well as the significance of accounting for confounders in studies that are not randomized. The report stresses the need for a priori definition of confounders based on scientific literature and, where necessary, their validation by clinical experts. Accordingly, this project aimed to carry out a systematic literature review (SLR) to identify potential confounders in this clinical area, outlined in national and international guidelines, recommendations, and publications, and validate them with clinical experts, to assist Roche in analyzing the data for the benefit assessment of Evrysdi (risdiplam), ensuring compliance with the evidence development requirements in Germany.

2. Methodology

2.1 Overview and Objectives

This project was conducted in two distinct phases; the first phase, consisting of two individual steps, involved the systematic identification of evidence-based guidelines and recommendations (step 1), as well as systematic reviews and meta-analyses (step 2), that reported potential confounders in the indication of SMA, through literature searching in relevant databases. The second phase focused on the validation of these confounders through engagement with key opinion leaders (KOLs). Figure 1 provides an overview of the two phases, with further details presented below: identification of confounders through the SLR, and validation of confounders via expert input.

Phase 1: Identification of Confounders

- **Objective:** To systematically identify evidence-based guidelines and recommendations, as well as systematic review and meta-analyses studies, that report potential confounders in the indication of SMA.
- **Tasks:**
  - Develop appropriate inclusion and exclusion criteria to ensure the relevance and quality of the data collected;
  - Conduct a comprehensive literature review in pre-specified databases to identify existing guidelines, recommendations, and non-randomized studies that report confounders;
  - Create a database or spreadsheet to organize and catalog the confounders identified during the literature review;
  - Summarize findings in a preliminary report that lists all potential confounders extracted from the literature review.

Phase 2: Validation of the Confounders

- **Objective:** To validate the identified confounders through expert input via interviews and/or a workshop (or via email).
- **Tasks:**
  - Identify and recruit KOLs in the field, ensuring a broad representation of expertise.
  - Design and plan interviews or a workshop with these KOLs to discuss and validate the identified confounders.

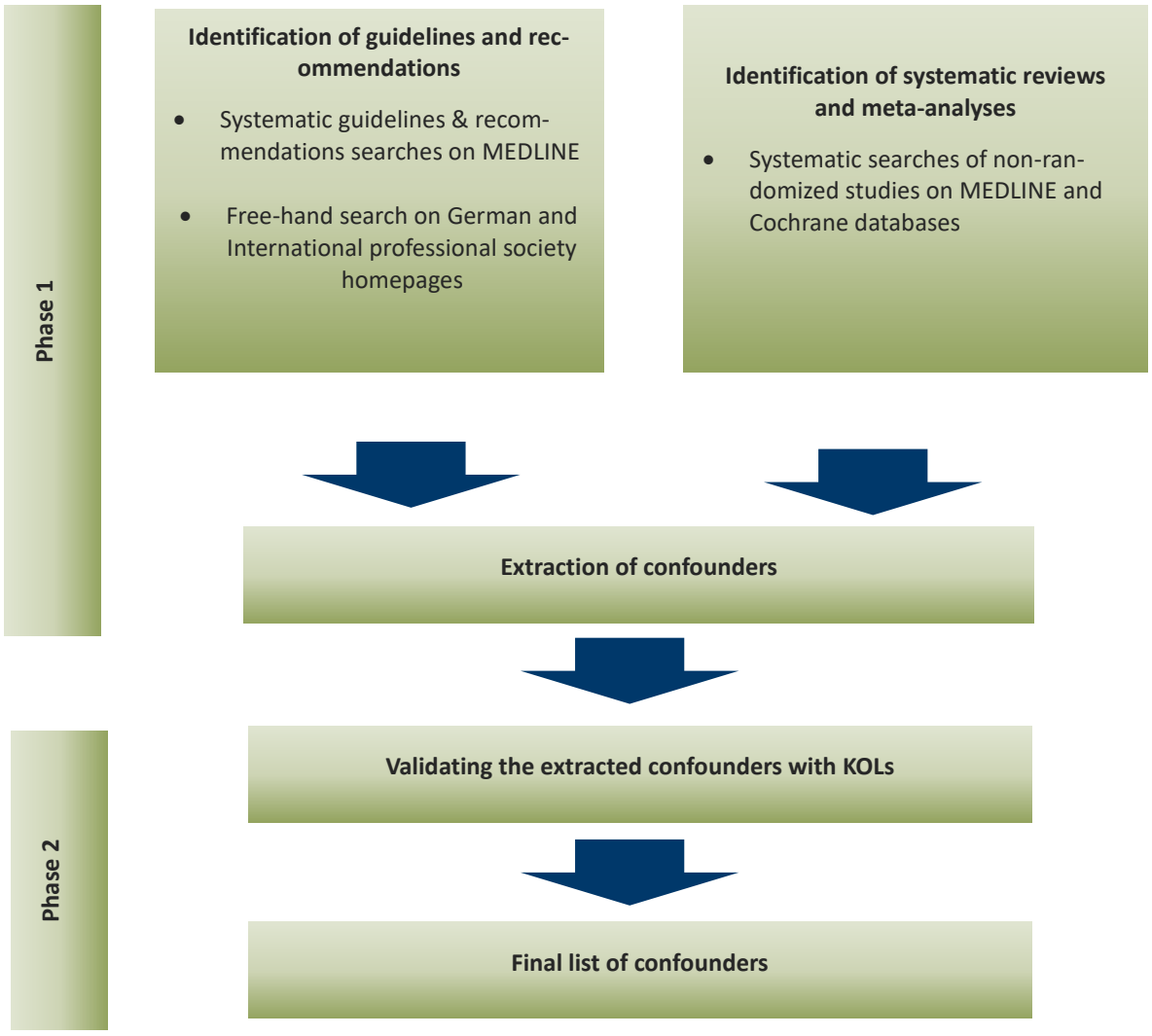
➢ Develop interview guides or workshop materials focusing on the evaluation of the relevance and impact of each identified confounder.

➢ Conduct the interviews or workshop, collecting detailed feedback from the KOLs.

➢ Analyze the feedback to determine which confounders are most significant and relevant according to expert consensus.

➢ Finalize report following input from KOLs.

Figure 1: Overview of methodology in this study



2.2 Phase 1: Identification of Confounders

2.2.1 Scope for the review

The review aimed to conduct an SLR to identify potential confounders cited in national and international guidelines, recommendations, and publications (systematic reviews and meta-analyses). The review process is integral to the broader scope of this research, and involves an identification of potential confounders as detailed in relevant guidelines and publications across various regions. The aim is to ensure a comprehensive understanding and precise accounting of confounding variables in SMA clinical research contexts.

To fulfil the requirements for identifying confounders in non-randomized studies, a two-step methodological approach was employed. In step 1, evidence-based guidelines and recommendations were identified through a systematic search of the MEDLINE bibliographic database. Subsequently, a supplementary structured free-hand search was carried out across various databases and on specific websites of German and international professional societies. In step 2, a systematic search was performed in the bibliographic databases MEDLINE and the Cochrane Database to identify full-text publications of systematic reviews and meta-analyses in the indication of SMA.

2.2.2 Data sources

The bibliographic databases used for systematic information retrieval included MEDLINE (PubMed) and the Cochrane Library (Cochrane Database of Systematic Reviews), with supplementary free-hand searching performed to ensure that all relevant records were identified.

2.2.2.1 Guidelines and recommendations

The bibliographic search was conducted within the MEDLINE bibliographic database using an appropriate search strategy. Details of the search strategy can be found in Annex 1.
Additionally, a structured free-hand search was performed across various databases and websites. Each search strategy was individually adapted to suit the specific requirements of the respective databases and websites. This search took place in the following databases and organization websites: Association of the Scientific Medical Societies (AWMF), Canadian Medical Association (CMA) Infobase, Turning Research Into Practice (TRIP) Database, and Google Scholar. Additionally, a general internet search was executed to identify current guidelines from German organizations, including Gesellschaft für Neuropädiatrie and Deutsche Gesellschaft für Muskelkranke e.V., as well as international bodies including Translational Research in Europe for the Assessment and Treatment of Neuromuscular Disease (Treat-NMD), Neuromuscular Network, SMA Europe, and Cure SMA. Searches also covered the PubMed database to ensure comprehensive coverage.

2.2.2.2 Systematic reviews and Meta-analyses

This search was conducted within the MEDLINE bibliographic database and the Cochrane Database of Systematic Reviews. The search strategies were individually tailored and structured for each database. Detailed descriptions of the search strategies can be found in Annex 1 and Annex 2.

2.2.3 Search strategies

The search strings used were designed in a manner analogous to the evidence search conducted by the Federal Joint Committee (Gemeinsamer Bundesausschuss, GBA). The search strategies employed a combination of relevant controlled vocabulary and natural language to strike a balance between sensitivity and specificity. All search terms used for each included database are documented in Annex 1 and Annex 2.

2.2.4 Inclusion criteria

2.2.4.1 Types of study to be included

The records eligible for inclusion can be classified into two publication types: (I) current valid versions of evidence-based guidelines and recommendations, and (II) full-text publications of systematic reviews and meta-analyses. Both record types should be related to the indication of SMA.

2.2.4.2 Population

The population of interest for this review comprised patients diagnosed with SMA (entire indication included for the guidelines and recommendations review), with the inclusion criteria detailed for different patient groups with an SMA diagnosis for the systematic reviews and meta-analyses review:

- **Presymptomatic Patients:** These include individuals with 5q-associated SMA who have a biallelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene.

- **Symptomatic Patients:** This group is further subdivided based on the type of SMA:

➢ Patients with a biallelic mutation in the *SMN1* gene and clinically diagnosed type 1 SMA.

➢ Patients with a biallelic mutation in the *SMN1* gene and clinically diagnosed type 2 SMA, who also have up to three copies of the *SMN2* gene.

➢ Patients with a biallelic mutation in the SMN1 gene and clinically diagnosed type 3 SMA, who also have up to three copies of the SMN2 gene.

2.2.4.3 Interventions

There were no limitations on the types of interventions to be included in the studies reviewed. This approach allowed for a broad scope of analysis covering various treatment methods and care strategies for SMA.

2.2.4.4 Comparators

There were no restrictions on the comparators to be included. This inclusion criterion ensured that all potential comparative analyses relevant to SMA treatments and outcomes were considered.

2.2.4.5 Outcomes

The objective of this review was to identify and synthesize evidence that provides insight into key endpoints such as confounders, risk factors, and prognostic factors associated with SMA.

Guidelines and Recommendations Review: Guidelines and recommendations should include information on prognostic factors relevant to SMA.

Systematic Reviews and Meta-Analyses Review: The studies should report data on at least one patient-relevant outcome across the following dimensions:

- Mortality: Documentation of deaths.
- Morbidity: Assessment includes motor function, which should be evaluated using age-appropriate instruments based on disease severity, notably the achievement of world health organization (WHO) motor development milestones. Respiratory function considerations include the need for permanent ventilation. Bulbar function is assessed by the ability to swallow and speak and the necessity for non-oral nutritional support. Other complications such as pain and orthopaedic issues should also be reported.
- Side-effects: Recording of adverse events.
- Health-related Quality-of-Life: Measurement of health-related quality-of-life using an age-appropriate assessment instrument.

These criteria ensured a comprehensive inclusion of outcomes that are critical for managing SMA effectively.

2.2.4.6 Country

There were no geographic limitations on the studies included in this review. Studies that met the inclusion criteria and were conducted in any country were eligible for inclusion. This approach ensured a broad and diverse range of data sources, enhancing the comprehensiveness of the review.

2.2.4.7 Language

Only studies published in full text in English or German were included in the review. Studies with abstracts in English or German but with full texts in other languages were excluded.

2.2.4.8 Publication timeframe

All studies published from the inception of the database to the present were included in this review. This approach was intended to capture all available evidence, providing a comprehensive overview of the research conducted within the specified timeframe.

2.2.5 Exclusion criteria

For the review of systematic reviews and meta-analyses, specific study types were excluded from consideration. These included Health Technology Assessment (HTA) reports, dose-finding studies, non-interventional studies, narrative reviews, case reports, retrospective studies and cohort studies, opinion pieces, and animal studies or in vitro studies. Additionally, only documents that were available as full-text publications were included. Conference abstracts or presentations that did not provide full-text access were excluded.

2.2.6 Screening of records

The screening of records was conducted by two independent reviewers. This process included an initial screening of titles and abstracts according to pre-specified inclusion and exclusion criteria, which was then followed by a comprehensive full-text screening procedure.
A 'search diary' was maintained to document the databases searched, the keywords used, and the outcomes of these searches. Titles and abstracts of studies deemed potentially relevant were logged using the Rayyan.ai online tool (https://www.rayyan.ai/), with notes on the source of each reference. Decisions regarding inclusion or exclusion were also recorded in this database. Two independent reviewers then carried out the screening of the retrieved results.

2.2.6.1 First screening

Titles and abstracts of all records retrieved through the electronic search were assessed. This initial screening was conducted by two independent reviewers who excluded any articles that were unrelated to the review question. Discrepancies between the reviewers' decisions were resolved through discussion. If a consensus could not be reached, a third reviewer was consulted to make the final decision.

2.2.6.2 Second screening

When studies potentially met the inclusion criteria based on their title and abstract, or if the abstract lacked sufficient information to make a decision, two review authors assessed the full text of the articles. Any disagreements between the reviewers' decisions were resolved through discussion. If consensus was not reached, a third reviewer was consulted. The reasons for excluding studies at this stage was documented. The outcomes of these reviews were reported in accordance with the PRISMA statement (Page et al., 2021).

2.2.7 Data extraction

Data from all included studies were extracted using a pre-designed and validated data extraction form developed in Microsoft Excel. The data elements extracted included, but were not limited to, study title and year of publication, sponsor (if applicable), countries of study execution, study setting, study population, inclusion/exclusion criteria, baseline characteristics, study methodology, results, potential confounding factors, risk factors, and prognostic factors.
The data extraction was conducted by one reviewer and verified by a second independent reviewer to ensure accuracy. Any discrepancies between the reviewers were resolved through discussion and, if necessary, by consulting a third review author. In cases of incomplete or missing data, the authors of the respective studies were contacted for clarification. The main findings from this data extraction process were summarized in 'Summary of Included Studies' tables.

2.3 Phase 2: Validation of Confounders

Phase 2 of the project was dedicated to verifying the relevance of confounders that had been identified from various sources such as national and international guidelines and recommendations, as well as systematic reviews and meta-analyses studies related to SMA. This phase began following the extraction of confounders deemed potentially relevant from the literature. These confounders were further evaluated for their impact and importance to the target population.

The methodology of this phase involved identifying a group of KOLs from the SMA field, who bring a diverse range of expertise to the project. The activities of this phase include detailed planning and execution of interviews (via email or virtual) or workshop with these KOLs. The objective was to engage in thorough discussions and critical evaluations of each confounder’s relevance and potential impact on SMA research, particularly with a view to assisting Roche in analyzing the data for the benefit assessments of Evrysdi (risdiplam) in Germany. These interactions were structured and guided utilizing meticulously prepared materials, which were designed to aid in a comprehensive examination of each confounder.

Feedback collected from these expert discussions was methodically analyzed to identify which confounders are considered most significant and relevant, based on a

consensus among the experts. This feedback is instrumental in refining the focus of the research and ensuring its applicability to real-world settings.

From a clinical perspective, the identified confounders were categorized into three distinct groups, reflecting their impact on research outcomes:

- **Very Important**: This category includes confounders that are essential for adjusting non-randomized studies. These are critical elements that must be accounted for to ensure the validity of the study results.
- **Less Important**: Confounders in this group may marginally affect study outcomes. While it is beneficial to control these confounders if feasible, their absence does not compromise the overall validity of the study.
- **Not Important**: These are confounders that are considered irrelevant to the study due to their specific characteristics, such as being study endpoints themselves or related to the particular settings of the study.

This classification helped to streamline the research process by prioritizing the most important confounders and identifying those that can be considered less critical. The outcomes of this phase provide a clearer understanding of the factors that Roche need to take into account when conducting any statistical analysis for Evrysdi (risdiplam) for GB-A submission in Germany, leading to more accurate and reliable results and evidence.

3. Results

3.1 Phase 1: Identification of Confounders

Guidelines

The PRISMA diagram shown in Figure 2 illustrates the screening and selection process for relevant guidelines and recommendations, which form the basis for the identification of confounders. The search yielded 52 hits in the MEDLINE bibliographic database. In the structured free-hand search, 62 potentially relevant publications were identified. After excluding duplicates, 53 hits remained to be evaluated via the 2-step selection/screening procedure.

During the first stage of screening, non-relevant publications were excluded based on title and abstract by checking for population, study type and language. In total, 61 publications were excluded. In the second screening stage, full texts of publications remaining from the first stage (53 hits) were reviewed and checked for relevance. In addition to the criteria from the first screening stage, the full texts were also checked for information on prognostic endpoints. As a result, a total of 21 evidence-based guidelines and recommendations publications related to the indication of SMA were included.

Figure 2 : PRISMA diagram-guidelines and recommendations review

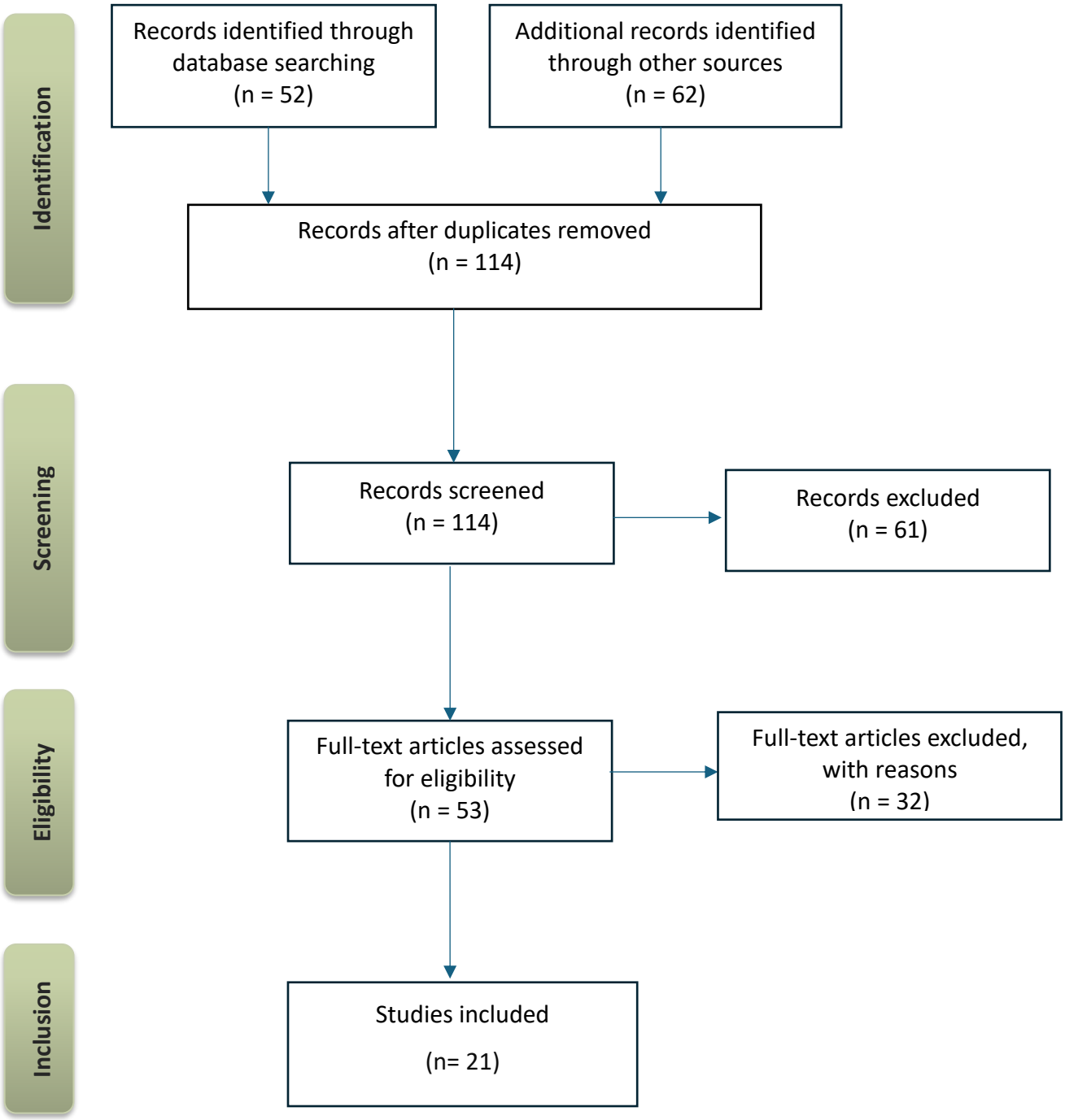


Table 2: List of guidelines reviewed in full-text stage and excluded with reason

No	Study title	Reason for exclusion
1	Deignan, J. L., Astbury, C., Behlmann, A., Guha, S., Monaghan, K. G., Reddi, H. V, Seifert, B. A., Tayeh, M., & Wakeling, E. (2021). Addendum: Technical standards and guidelines for spinal muscular atrophy testing. Genet Med, 23(12), 2462.	Study type not fulfilled
2	Glascock, J., Sampson, J., Connolly, A. M., Darras, B. T., Day, J. W., Finkel, R., Howell, R. R., Klinger, K. W., Kuntz, N., Prior, T., Shieh, P. B., Crawford, T. O., Kerr, D., & Jarecki, J. (2020). Revised Recommendations for the Treatment of Infants Diagnosed with Spinal Muscular Atrophy Via Newborn Screening Who Have 4 Copies of SMN2. J Neuromuscul Dis, 7(2), 97–100.	Duplicate
3	Hagenacker, T., Hermann, A., Kamm, C., Walter, M. C., Weiler, M., Günther, R., Wurster, C. D., & Kleinschnitz, C. (2019). [Spinal Muscular Atrophy - expert recommendations for the use of nusinersen in adult patients]. Fortschr Neurol Psychiatr, 87(12), 703–710. https://doi.org/10.1055/a-0996-0994 %(Spinale Muskelatrophie – Expertenempfehlungen zur Behandlung von erwachsenen Patienten mit Nusinersen.	Study type not fulfilled
4	Ivanov, I., Atkinson, D., Litvinenko, I., Angelova, L., Andonova, S., Mumdjiev, H., Pacheva, I., Panova, M., Yordanova, R., Belovejdov, V., Petrova, A., Bosheva, M., Shmilev, T., Savov, A., & Jordanova, A. (2018). Pontocerebellar hypoplasia type 1 for the neuropediatrician: Genotype-phenotype correlations and diagnostic guidelines based on new cases and overview of the literature. Eur J Paediatr Neurol, 22(4), 674–681.	Study type not fulfilled
5	Kichula, E. A., Proud, C. M., Farrar, M. A., Kwon, J. M., Saito, K., Desguerre, I., & McMillan, H. J. (2021). Expert recommendations and clinical considerations in the use of onasemnogene abeparvovec gene therapy for spinal muscular atrophy. Muscle Nerve, 64(4), 413–427. https://doi.org/10.1002/mus.27363	Duplicate
6	Kirschner, J., Butoianu, N., Goemans, N., Haberlova, J., Kostera-Pruszczyk, A., Mercuri, E., van der Pol, W. L., Quijano-Roy, S., Sejersen, T., Tizzano, E. F., Ziegler, A., Servais, L., & Muntoni, F. (2020). European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy. Eur J Paediatr Neurol, 28, 38–43. https://doi.org/10.1016/j.ejpn.2020.07.001	Study type not fulfilled
7	Kooi-van Es, M., Erasmus, C. E., Voet, N. B. M., van den Engel-Hoek, L., & van der Wees, P. J. (2024). Best practice recommendations for speech-language pathology in children with neuromuscular disorders: A Delphi-based consensus study. Int J Speech Lang Pathol, 26(1), 45–58. https://doi.org/10.1080/17549507.2023.2181224	Endpoints not fulfilled
8	Lyu, F., Zheng, C., Wang, H., Nie, C., Ma, X., Xia, X., Zhu, W., Jin, X., Hu, Y., Sun, Y., Zhu, Y., Kuwabara, S., Cortese, R., Maqbool Hassan, K., Takai, K., Paredes, I., Webere, R., Turk, M., Kimura, J., & Jiang, J. (2020). Establishment of a clinician-led guideline on the diagnosis and treatment of Hirayama disease using a modified Delphi technique. Clin Neurophysiol, 131(6), 1311–1319. https://doi.org/10.1016/j.clinph.2020.02.022	Study type not fulfilled

9	McMillan, H. J., Kernohan, K. D., Yeh, E., Amburgey, K., Boyd, J., Campbell, C., Dowling, J. J., Gonorazky, H., Marcadier, J., Tarnopolsky, M. A., Vajsar, J., MacKenzie, A., & Chakraborty, P. (2021). Newborn Screening for Spinal Muscular Atrophy: Ontario Testing and Follow-up Recommendations. Can J Neurol Sci, 48(4), 504–511. https://doi.org/10.1017/cjn.2020.229	Study type not fulfilled
10	Mercuri, E., Finkel, R. S., Muntoni, F., Wirth, B., Montes, J., Main, M., Mazzone, E. S., Vitale, M., Snyder, B., Quijano-Roy, S., Bertini, E., Davis, R. H., Meyer, O. H., Simonds, A. K., Schroth, M. K., Graham, R. J., Kirschner, J., Iannaccone, S. T., Crawford, T. O., … Sejersen, T. (2018). Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord, 28(2), 103–115. https://doi.org/10.1016/j.nmd.2017.11.005	Endpoints not fulfilled
11	Ou, J. Y., Liu, J. J., Xu, J., Li, J. Y., Liu, Y., Liu, Y. Z., Lu, L. M., Pan, H. F., & Wang, L. (2023). Quality appraisal of clinical practice guidelines for motor neuron diseases or related disorders using the AGREE II instrument. Front Neurol, 14, 1180218. https://doi.org/10.3389/fneur.2023.1180218	Study type not fulfilled
12	Petri, S., Grehl, T., Grosskreutz, J., Hecht, M., Hermann, A., Jesse, S., Lingor, P., Löscher, W., Maier, A., Schoser, B., Weber, M., & Ludolph, A. C. (2023). Guideline “Motor neuron diseases” of the German Society of Neurology (Deutsche Gesellschaft für Neurologie). Neurol Res Pract, 5(1), 25. https://doi.org/10.1186/s42466-023-00251-x	Study type not fulfilled
13	Pradat, P. F., Bernard, E., Corcia, P., Couratier, P., Jublanc, C., Querin, G., Morélot Panzini, C., Salachas, F., Vial, C., Wahbi, K., Bede, P., & Desnuelle, C. (2020). The French national protocol for Kennedy’s disease (SBMA): consensus diagnostic and management recommendations. Orphanet J Rare Dis, 15(1), 90. https://doi.org/10.1186/s13023-020-01366-z	Endpoints not fulfilled
14	Sansone, V. A., Racca, F., Ottonello, G., Vianello, A., Berardinelli, A., Crescimanno, G., & Casiraghi, J. L. (2015). 1st Italian SMA Family Association Consensus Meeting: Management and recommendations for respiratory involvement in spinal muscular atrophy (SMA) types I-III, Rome, Italy, 30-31 January 2015. Neuromuscul Disord, 25(12), 979–989. https://doi.org/10.1016/j.nmd.2015.09.009	Study type not fulfilled
15	Silvinato, A., & Bernardo, W. M. (2018). Spinal muscular atrophy 5Q - Treatment with nusinersen. Rev Assoc Med Bras (1992), 64(6), 484–491. https://doi.org/10.1590/1806-9282.64.06.484	Endpoints not fulfilled
16	Trenkle, J., Brugman, J., Peterson, A., Roback, K., & Krosschell, K. J. (2021). Filling the gaps in knowledge translation: Physical therapy recommendations for individuals with spinal muscular atrophy compared to standard of care guidelines. Neuromuscul Disord, 31(5), 397–408. https://doi.org/10.1016/j.nmd.2021.02.011	Study type not fulfilled
17	Urushitani, M., Warita, H., Atsuta, N., Izumi, Y., Kano, O., Shimizu, T., Nakayama, Y., Narita, Y., Nodera, H., Fujita, T., Mizoguchi, K., Morita, M., & Aoki, M. (2024). The clinical practice guideline for the management of amyotrophic lateral sclerosis in Japan-update 2023. Rinsho Shinkeigaku, 64(4), 252–271. https://doi.org/10.5692/clinicalneurol.cn-001946	Endpoints not fulfilled
18	Walter, M. C., Laforêt, P., van der Pol, W. L., & Pegoraro, E. (2023). 254th ENMC international workshop. Formation of a European network to initiate a European data collection, along with development and sharing of treatment guidelines for adult SMA	Study type not fulfilled

	patients. Virtual meeting 28 - 30 January 2022. Neuromuscul Disord, 33(6), 511–522. https://doi.org/10.1016/j.nmd.2023.03.011 Writing Group For Practice Guidelines For, D., Treatment Of Genetic Diseases Medical Genetics Branch Of Chinese Medical, A., Pan, J., Tan, H., Zhou, M., Liang, D., & Wu, L. (2020). [Clinical practice guidelines for spinal muscular atrophy]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi, 37(3), 263–268. https://doi.org/10.3760/cma.j.issn.1003-9406.2020.03.007	
19	Ziegler, A., Wilichowski, E., Schara, U., Hahn, A., Müller-Felber, W., Johannsen, J., von der Hagen, M., von Moers, A., Stoltenburg, C., Saffari, A., Walter, M. C., Husain, R. A., Pechmann, A., Köhler, C., Horber, V., Schwartz, O., & Kirschner, J. (2020). [Recommendations for gene therapy of spinal muscular atrophy with onasemnogene abeparvovec-AVXS-101 : Consensus paper of the German representatives of the Society for Pediatric Neurology (GNP) and the German treatment centers with collaboration of the medical scientific advisory board of the German Society for Muscular Diseases (DGM)]. Nervenarzt, 91(6), 518–529.	Study type not fulfilled
20	Handlungsempfehlungen zur Gentherapie der spinalen Muskelatrophie mit Onasemnogene Abeparvovec – AVXS-101 : Konsensuspapier der deutschen Vertretung der Gesellschaft für Neuropädiatrie (GNP) und der deutschen Behandlungszentren unter Mitwirkung des Medizinisch-Wissenschaftlichen Beirates der Deutschen Gesellschaft für Muskelkranke (DGM) e. V.	Study type not fulfilled
21	Bergin S, Mockford C. Recommendations to support informal carers of people living with motor neurone disease. Br J Community Nurs. 2016 Oct 2;21(10):518-524. doi: 10.12968/bjcn.2016.21.10.518. PMID: 27715256.	Study type not fulfilled
22	Expert Panel on Neurological Imaging; Harvey HB, Watson LC, Subramaniam RM, Burns J, Bykowski J, Chakraborty S, Ledbetter LN, Lee RK, Pannell JS, Pollock JM, Powers WJ, Rosenow JM, Shih RY, Slavin K, Utukuri PS, Corey AS. ACR Appropriateness Criteria® Movement Disorders and Neurodegenerative Diseases. J Am Coll Radiol. 2020 May;17(5S):S175-S187. doi: 10.1016/j.jacr.2020.01.042. PMID: 32370961.	Study type not fulfilled
23	Mercuri, E., Finkel, R.S., Muntoni, F., Wirth, B., Montes, J., Main, M., Mazzone, E.S., Vitale, M., Snyder, B., Quijano-Roy, S. and Bertini, E., 2018. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscular disorders*, *28*(2), pp.103-115.	Duplicate
24	Cuscó, I., Bernal, S., Blasco-Pérez, L., Calucho, M., Alias, L., Fuentes-Prior, P., & Tizzano, E. F. (2020). Practical guidelines to manage discordant situations of SMN2 copy number in patients with spinal muscular atrophy. *Neurology: Genetics*, *6*(6), e530.	Duplicate
25	Glascock, J., Sampson, J., Haidet-Phillips, A., Connolly, A., Darras, B., Day, J., Finkel, R., Howell, R. R., Klinger, K., & Kuntz, N. (2018). Treatment algorithm for infants diagnosed with spinal muscular atrophy through newborn screening. Journal of Neuromuscular Diseases, 5(2), 145–158.	Duplicate
26	Gallo, J.M., 2004. Spinobulbar muscular atrophy (Kennedy's disease). In *Handbook of Clinical Neurophysiology* (Vol. 4, pp. 403-417). Elsevier.	Endpoints not fulfilled

27	McMillan, H.J., Kernohan, K.D., Yeh, E., Amburgey, K., Boyd, J., Campbell, C., Dowling, J.J., Gonorazky, H., Marcadier, J., Tarnopolsky, M.A. and Vajsar, J., 2021. Newborn screening for spinal muscular atrophy: Ontario testing and follow-up recommendations. Canadian Journal of Neurological Sciences, 48(4), pp.504-511.	Study type not fulfilled
28	Lee, B.H., Waldrop, M.A., Connolly, A.M. and Ciafaloni, E., 2021. Time is muscle: A recommendation for early treatment for preterm infants with spinal muscular atrophy. Muscle & Nerve, 64(2), pp.153-155.	Duplicate
29	Kichula, E.A., Proud, C.M., Farrar, M.A., Kwon, J.M., Saito, K., Desguerre, I. and McMillan, H.J., 2021. Expert recommendations and clinical considerations in the use of onasemnogene abeparvovec gene therapy for spinal muscular atrophy. *Muscle & Nerve*, *64*(4), pp.413-427.	Duplicate
30	Amira Chadid-Stetter Drug therapy for respiratory distress in children with severe spinal muscular atrophy type 1. Dissertation. 2022	Study type not fulfilled
31	Martin et al,. Certified further training Spinal muscular atrophy, 2022	Study type not fulfilled
32	DGM - Federal Office. Spinobulbar muscular atrophy type Kennedy (SBMA)	Endpoints not fulfilled

Table 3: List of included guidelines and recommendations

No	Study title
1	Abiusi, E., Vaisfeld, A., Fiori, S., Novelli, A., Spartano, S., Faggiano, M. V, Giovanniello, T., Angeloni, A., Vento, G., Santoloci, R., Gigli, F., D'Amico, A., Costa, S., Porzi, A., Panella, M., Ticci, C., Daniotti, M., Sacchini, M., Boschi, I., … Tiziano, F. D. (2023). Experience of a 2-year spinal muscular atrophy NBS pilot study in Italy: towards specific guidelines and standard operating procedures for the molecular diagnosis. J Med Genet, 60(7), 697–705. https://doi.org/10.1136/jmg-2022-108873
2	Amin, R., MacLusky, I., Zielinski, D., Adderley, R., Carnevale, F., Chiang, J., Côté, A., Daniels, C., Daigneault, P., & Harrison, C. (2017). Pediatric home mechanical ventilation: a Canadian Thoracic Society clinical practice guideline executive summary. Canadian Journal of Respiratory, Critical Care, and Sleep Medicine, 1(1), 7–36.
3	Cuscó, I., Bernal, S., Blasco-Pérez, L., Calucho, M., Alias, L., Fuentes-Prior, P., & Tizzano, E. F. (2024). Practical guidelines to manage discordant situations of SMN2 copy number in patients with spinal muscular atrophy. Neurol Genet, 6(6), e530.
4	Palmer, K., Tuira, L., Reise, K., Alzadjali, A., & Mckinnon, N. (2022). PP232 [Healthcare systems » Capacity building]: collaborative interprofessional guideline development: advancing critical care for children with spinal muscular atrophy and their families . Paediatric Critical Care Medicine.
5	Glascock, J., Sampson, J., Haidet-Phillips, A., Connolly, A., Darras, B., Day, J., Finkel, R., Howell, R. R., Klinger, K., & Kuntz, N. (2020). Treatment algorithm for infants diagnosed with spinal muscular atrophy through newborn screening. Journal of Neuromuscular Diseases, 5(2), 145–158.
6	Hagenacker, T., Hermann, A., Kamm, C., Walter, M. C., Weiler, M., Günther, R., Wurster, C. D., & Kleinschnitz, C. (2019). [Spinal Muscular Atrophy - expert recommendations for the use of nusinersen in

	adult patients]. Fortschr Neurol Psychiatr, 87(12), 703–710. https://doi.org/10.1055/a-0996-0994 %(Spinale Muskelatrophie – Expertenempfehlungen zur Behandlung von erwachsenen Patienten mit Nusinersen.
7	Kichula, E. A., Proud, C. M., Farrar, M. A., Kwon, J. M., Saito, K., Desguerre, I., & McMillan, H. J. (2021). Expert recommendations and clinical considerations in the use of onasemnogene abeparvovec gene therapy for spinal muscular atrophy. Muscle Nerve, 64(4), 413–427.
8	Mercuri, E., Finkel, R. S., Muntoni, F., Wirth, B., Montes, J., Main, M., Mazzone, E. S., Vitale, M., Snyder, B., Quijano-Roy, S., Bertini, E., Davis, R. H., Meyer, O. H., Simonds, A. K., Schroth, M. K., Graham, R. J., Kirschner, J., Iannaccone, S. T., Crawford, T. O., … Sejersen, T. (2018). Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord, 28(2), 103–115.
9	Milligan, J. N., Blasco-Pérez, L., Costa-Roger, M., Codina-Solà, M., & Tizzano, E. F. (2022). Recommendations for Interpreting and Reporting Silent Carrier and Disease-Modifying Variants in SMA Testing Workflows. Genes (Basel), 13(9). https://doi.org/10.3390/genes13091657
10	Oliver, D., Radunovic, A., Allen, A., & McDermott, C. (2017). The development of the UK National Institute of Health and Care Excellence evidence-based clinical guidelines on motor neurone disease. Amyotroph Lateral Scler Frontotemporal Degener, 18(5), 313–323.
11	Castellano P, I., Cabrera-Serrano, M., Calvo Medina, R., Cattinari, M. G., Espinosa García, S., Fernández-Ramos, J. A., García Campos, O., Gómez-Andrés, D., Grimalt Calatayud, M. A., Gutiérrez Martínez, A. J., Ibáñez Albert, E., Kapetanovic García, S., Madruga-Garrido, M., Martínez-Moreno, M., Medina Cantillo, J., Melián Suárez, A. I., Moreno Escribano, A., Munell, F., Nascimento Osorio, A., … Vázquez-Costa, J. F. (2022). Delphi consensus on recommendations for the treatment of spinal muscular atrophy in Spain (RET-AME consensus). Neurologia (Engl Ed), 37(3), 216–228. https://doi.org/10.1016/j.nrleng.2021.07.002
12	Solé, G., Salort-Campana, E., Pereon, Y., Stojkovic, T., Wahbi, K., Cintas, P., Adams, D., Laforet, P., Tiffreau, V., Desguerre, I., Pisella, L. I., Molon, A., & Attarian, S. (2020). Guidance for the care of neuromuscular patients during the COVID-19 pandemic outbreak from the French Rare Health Care for Neuromuscular Diseases Network. Rev Neurol (Paris), 176(6), 507–515. https://doi.org/10.1016/j.neurol.2020.04.004
13	Ziegler, A., Wilichowski, E., Schara, U., Hahn, A., Müller-Felber, W., Johannsen, J., von der Hagen, M., von Moers, A., Stoltenburg, C., Saffari, A., Walter, M. C., Husain, R. A., Pechmann, A., Köhler, C., Horber, V., Schwartz, O., & Kirschner, J. (2020). [Recommendations for gene therapy of spinal muscular atrophy with onasemnogene abeparvovec-AVXS-101 : Consensus paper of the German representatives of the Society for Pediatric Neurology (GNP) and the German treatment centers with collaboration of the medical scientific advisory board of the German Society for Muscular Diseases (DGM)]. Nervenarzt, 91(6), 518–529.
14	Handlungsempfehlungen zur Gentherapie der spinalen Muskelatrophie mit Onasemnogene Abeparvovec – AVXS-101 : Konsensuspapier der deutschen Vertretung der Gesellschaft für Neuropädiatrie (GNP) und der deutschen Behandlungszentren unter Mitwirkung des Medizinisch-Wissenschaftlichen Beirates der Deutschen Gesellschaft für Muskelkranke (DGM) e. V.
15	NICE, N. (2016). Motor neurone disease: assessment and management. NICE Guidel NG42 Methods, Evid Recomm.

16	Michelson, D., Ciafaloni, E., Ashwal, S., Lewis, E., Narayanaswami, P., Oskoui, M., & Armstrong, M. J. (2018). Evidence in focus: Nusinersen use in spinal muscular atrophy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology, 91(20), 923–933.
17	Lee, B.H., Waldrop, M.A., Connolly, A.M. and Ciafaloni, E., 2021. Time is muscle: A recommendation for early treatment for preterm infants with spinal muscular atrophy. Muscle & Nerve, 64(2), pp.153-155.
18	Kölbel H., Müller-Felber W (2022). Spinale Muskelatrophie (SMA), Diagnostik und Therapie Entwicklungsstörungen
19	Nennstiel, U., Genzel-Boroviczény, O., Odenwald, B., Ensenauer, R., Rossi, R., Hoffmann, G. F., Schäfer-Graf, U., Blankenstein, O., Streffing, J., & GPP, J. H. (2020). Neugeborenen-Screening auf angeborene Stoffwechselstörungen, Endokrinopathien, schwere kombinierte Immundefekte (SCID) und Mukoviszidose. S2k-Leitlinie. AWMF Nr, 12–24.
20	Ludolph et al. (2021) LoMotor neurone diseases
21	Finkel, R. S., Mercuri, E., Meyer, O. H., Simonds, A. K., Schroth, M. K., Graham, R. J., Kirschner, J., Iannaccone, S. T., Crawford, T. O., & Woods, S. (2018). Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscular Disorders, 28(3), 197–207.

Systematic reviews and meta-analyses

The PRISMA diagram shown in Figure 3 illustrates the screening and selection process for relevant systematic reviews and meta-analyses, which forms the second basis for the identification of confounders. The search yielded 350 hits in the MEDLINE bibliographic database and 40 hits were identified in the Cochrane Library. After excluding duplicates, 390 hits remained to be evaluated via the 2-step selection/screening procedure. During the first stage of screening, non-relevant publications were excluded based on title and abstract by checking for population, endpoints, study type, documentation type and language. In total, 256 publications were excluded. In the second stage of screening, full texts of publications remaining from the first screening (124 hits) were reviewed and checked for relevance. As a result, 39 systematic review/meta-analyses publications were included for the indication.

Figure 3: PRISMA diagram- systematic reviews and meta-analysis

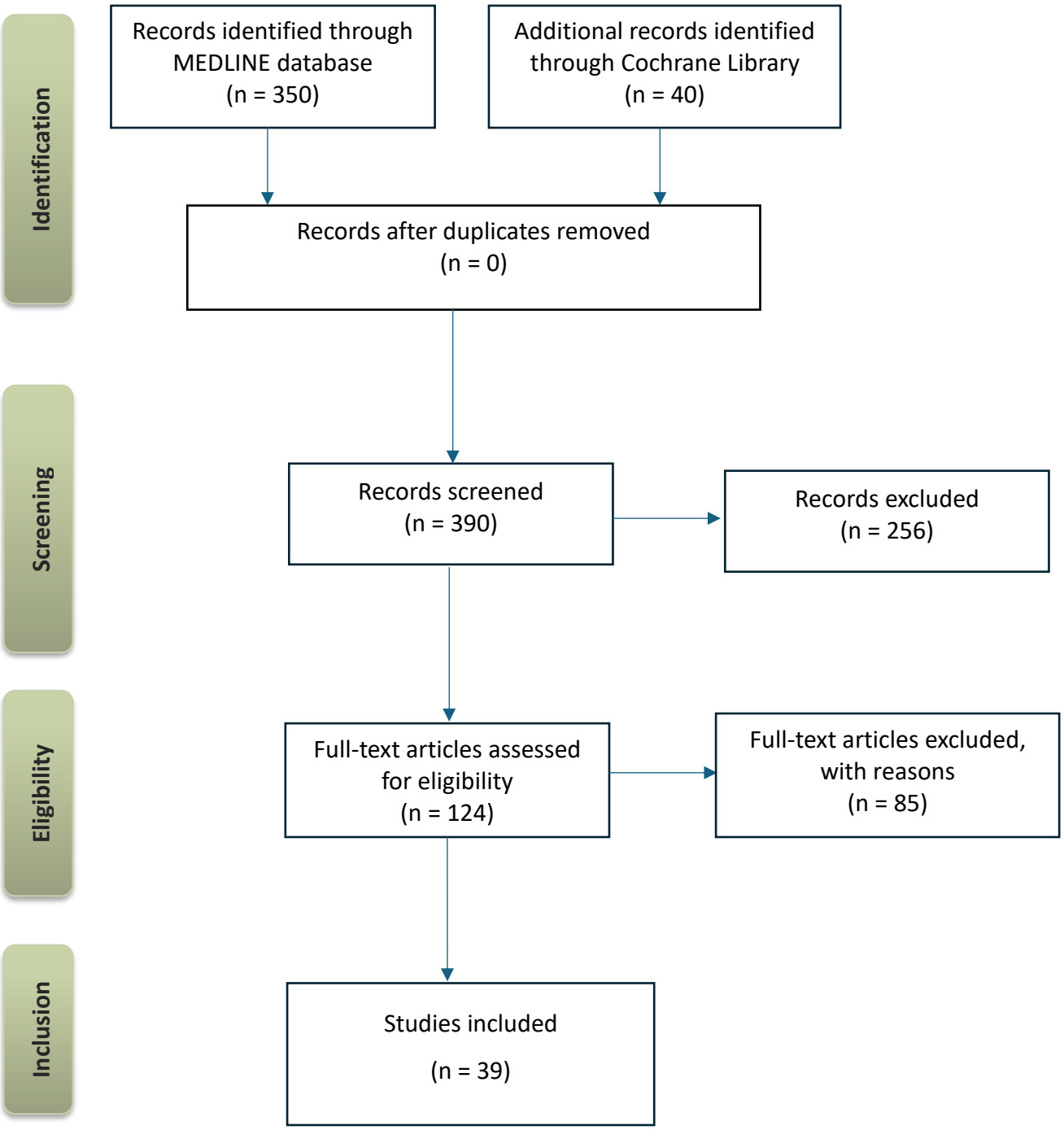


Table 4: List of systematic reviews and meta-analyses reviewed in full-text and excluded with reason

No.	Study title	Reason for exclusion
1	Zang, J. et al. DySMA - an Instrument to Monitor Swallowing Function in Children with Spinal Muscular Atrophy ages 0 to 24 Months: Development, Consensus, and Pilot Testing. J Neuromuscul Dis 11, 473–483 (2024).	Study type not fulfilled
2	Youn, B. Y. et al. Digital Biomarkers for Neuromuscular Disorders: A Systematic Scoping Review. Diagnostics (Basel) 11, (2021).	Patient population not fulfilled
3	Yin, J. et al. Application of exercise therapy in patients with chronic kidney disease-induced muscle atrophy: a scoping review. BMC Sports Sci Med Rehabil 16, 100 (2024).	Patient population not fulfilled
4	Yao, S. et al. Current Pharmacological Strategies for Duchenne Muscular Dystrophy. Front Cell Dev Biol 9, 689533 (2021).	Study type not fulfilled
5	Wei, X. et al. Notable Carrier Risks for Individuals Having Two Copies of SMN1 in Spinal Muscular Atrophy Families with 2-copy Alleles: Estimation Based on Chinese Meta-analysis Data. J Genet Couns 26, 72–78 (2017).	Endpoints not fulfilled
6	Wang, M. J. et al. Microglia in motor neuron disease: Signaling evidence from last 10 years. Dev Neurobiol 82, 625–638 (2022).	Study type not fulfilled
7	Waldboth, V., Patch, C., Mahrer-Imhof, R. & Metcalfe, A. Living a normal life in an extraordinary way: A systematic review investigating experiences of families of young people's transition into adulthood when affected by a genetic and chronic childhood condition. Int J Nurs Stud 62, 44–59 (2016).	Patient population not fulfilled
8	Vaidya, S. & Boes, S. Correction to: Measuring quality of life in children with spinal muscular atrophy: a systematic literature review. Qual Life Res 27, 3095 (2018).	Study type not fulfilled
9	Vaidya, S. & Boes, S. Measuring quality of life in children with spinal muscular atrophy: a systematic literature review. Qual Life Res 27, 3087–3094 (2018).	Endpoints not fulfilled
10	Uchitel, J., Kantor, B., Smith, E. C. & Mikati, M. A. Viral-Mediated Gene Replacement Therapy in the Developing Central Nervous System: Current Status and Future Directions. Pediatr Neurol 110, 5–19 (2020).	Study type not fulfilled
11	Tizzano, E. F. & Finkel, R. S. Spinal muscular atrophy: A changing phenotype beyond the clinical trials. Neuromuscul Disord 27, 883–889 (2017).	Study type not fulfilled
12	Slayter, J., Casey, L. & O'Connell, C. Patient Reported Outcome Measures in Adult Spinal Muscular Atrophy: A Scoping Review and Graphical Visualization of the Evidence. J Neuromuscul Dis 10, 239–250 (2023).	Endpoints not fulfilled

13	Simonds, A. K. Home Mechanical Ventilation: An Overview. Ann Am Thorac Soc 13, 2035–2044 (2016).	Study type not fulfilled
14	Silvinato, A. & Bernardo, W. M. Spinal muscular atrophy 5Q - Treatment with nusinersen. Rev Assoc Med Bras (1992) 64, 484–491 (2018).	Study type not fulfilled
15	Rao, V. K., Kapp, D. & Schroth, M. Gene Therapy for Spinal Muscular Atrophy: An Emerging Treatment Option for a Devastating Disease. J Manag Care Spec Pharm 24, S3-s16 (2018).	Study type not fulfilled
16	Quirke, M. B. et al. The factorial survey as an approach to investigate clinical decision-making: examining influences on a clinician's decision to initiate life-sustaining clinical technology for a child with spinal muscular atrophy type 1. Front Pediatr 11, 1252440 (2023).	Study type not fulfilled
17	Pradat, P. F. et al. The French national protocol for Kennedy's disease (SBMA): consensus diagnostic and management recommendations. Orphanet J Rare Dis 15, 90 (2020).	Study type not fulfilled
18	Petzold, A. The 2022 Lady Estelle Wolfson lectureship on neurofilaments. J Neurochem 163, 179–219 (2022).	Study type not fulfilled
19	Perez, B. A., Shutterly, A., Chan, Y. K., Byrne, B. J. & Corti, M. Management of Neuroinflammatory Responses to AAV-Mediated Gene Therapies for Neurodegenerative Diseases. Brain Sci 10, (2020).	Study type not fulfilled
20	Panagiotou, P., Kanaka-Gantenbein, C. & Kaditis, A. G. Changes in Ventilatory Support Requirements of Spinal Muscular Atrophy (SMA) Patients Post Gene-Based Therapies. Children (Basel) 9, (2022).	Study type not fulfilled
21	O'Sullivan, R., Carrier, J., Cranney, H. & Hemming, R. Effect of Lung Volume Recruitment on Pulmonary Function in Progressive Childhood-Onset Neuromuscular Disease: A Systematic Review. Arch Phys Med Rehabil 102, 976–983 (2021).	Patient population not fulfilled
22	Nidetz, N. F. et al. Adeno-associated viral vector-mediated immune responses: Understanding barriers to gene delivery. Pharmacol Ther 207, 107453 (2020).	Study type not fulfilled
23	Navarrete-Opazo, A., Garrison, S. & Waite, M. Molecular Biomarkers for Spinal Muscular Atrophy: A Systematic Review. Neurol Clin Pract 11, e524–e536 (2021).	Endpoints not fulfilled
24	Miladi, L. et al. Minimally Invasive Surgery for Neuromuscular Scoliosis: Results and Complications in a Series of One Hundred Patients. Spine (Phila Pa 1976) 43, E968-e975 (2018).	Patient population not fulfilled
25	Messina, S. et al. A critical review of patient and parent caregiver oriented tools to assess health-related quality of life, activity of daily living and caregiver burden in spinal muscular atrophy. Neuromuscul Disord 29, 940–950 (2019).	Endpoints not fulfilled

26	Mercuri, E. et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord 28, 103–115 (2018).	Duplicate
27	Mensch, S. M., Rameckers, E. A., Echteld, M. A. & Evenhuis, H. M. Instruments for the evaluation of motor abilities for children with severe multiple disabilities: A systematic review of the literature. Res Dev Disabil 47, 185–98 (2015).	Endpoints not fulfilled
28	Mahungu, A. C., Monnakgotla, N., Nel, M. & Heckmann, J. M. A review of the genetic spectrum of hereditary spastic paraplegias, inherited neuropathies and spinal muscular atrophies in Africans. Orphanet J Rare Dis 17, 133 (2022).	Patient population not fulfilled
29	McGrattan, K. E., Graham, R. J., DiDonato, C. J. & Darras, B. T. Dysphagia Phenotypes in Spinal Muscular Atrophy: The Past, Present, and Promise for the Future. Am J Speech Lang Pathol 30, 1008–1022 (2021).	Study type not fulfilled
30	López-Cortés, A., Echeverría-Garcés, G. & Ramos-Medina, M. J. Molecular Pathogenesis and New Therapeutic Dimensions for Spinal Muscular Atrophy. Biology (Basel) 11, (2022).	Study type not fulfilled
31	Long, C., Amoasii, L., Bassel-Duby, R. & Olson, E. N. Genome Editing of Monogenic Neuromuscular Diseases: A Systematic Review. JAMA Neurol 73, 1349–1355 (2016).	Patient population not fulfilled
32	Lin, A. Y. & Wang, L. H. Molecular Therapies for Muscular Dystrophies. Curr Treat Options Neurol 20, 27 (2018).	Study type not fulfilled
33	Li, D., McIntosh, C. S., Mastaglia, F. L., Wilton, S. D. & Aung-Htut, M. T. Neurodegenerative diseases: a hotbed for splicing defects and the potential therapies. Transl Neurodegener 10, 16 (2021).	Study type not fulfilled
34	Li, C. et al. The prevalence of spinal muscular atrophy carrier in China: Evidences from epidemiological surveys. Medicine (Baltimore) 99, e18975 (2020).	Endpoints not fulfilled
35	Krosschell, K. J. et al. Clinical and Research Readiness for Spinal Muscular Atrophy: The Time Is Now for Knowledge Translation. Phys Ther 102, (2022).	Study type not fulfilled
36	Kremer, L. S., Wortmann, S. B. & Prokisch, H. 'Transcriptomics': molecular diagnosis of inborn errors of metabolism via RNA-sequencing. J Inherit Metab Dis 41, 525–532 (2018).	Study type not fulfilled
37	Kilcher, G., Zwahlen, M., Ritter, C., Fenner, L. & Egger, M. Medical use of cannabis in Switzerland: analysis of approved exceptional licences. Swiss Med Wkly 147, w14463 (2017).	Endpoints not fulfilled
38	Jiménez-García, N. et al. Eosinophilic fasciitis in a pregnant woman with corticosteroid dependence and good response to infliximab. Rheumatol Int 41, 1531–1539 (2021).	Patient population not fulfilled

39	Jablonka, S. & Sendtner, M. Developmental regulation of SMN expression: pathophysiological implications and perspectives for therapy development in spinal muscular atrophy. Gene Ther 24, 506–513 (2017).	Study type not fulfilled
40	Iftikhar, M., Frey, J., Shohan, M. J., Malek, S. & Mousa, S. A. Current and emerging therapies for Duchenne muscular dystrophy and spinal muscular atrophy. Pharmacol Ther 220, 107719 (2021)	Study type not fulfilled
41	Hu, C. & Li, X. Gene therapeutic strategies and relevant clinical trials in neuromuscular disorder in China. Gene Ther 27, 321–328 (2020).	Study type not fulfilled
42	Hoo, F. K. et al. Androgen-modulating agents for spinal bulbar muscular atrophy/Kennedy's disease. Cochrane Database of Systematic Reviews (2022) doi:10.1002/14651858.CD012000.pub2.	Study type not fulfilled
43	Hoy, S. M. Nusinersen: A Review in 5q Spinal Muscular Atrophy. CNS Drugs 35, 1317–1328 (2021).	Study type not fulfilled
44	Hensel, N. & Claus, P. The Actin Cytoskeleton in SMA and ALS: How Does It Contribute to Motoneuron Degeneration? Neuroscientist 24, 54–72 (2018).	Study type not fulfilled
45	Grychtol, R., Abel, F. & Fitzgerald, D. A. The role of sleep diagnostics and noninvasive ventilation in children with spinal muscular atrophy. Paediatr Respir Rev 28, 18–25 (2018).	Study type not fulfilled
46	Grayev, A., Schoepp, M. & Kuner, A. A Systematic Review of Procedural Complications from Transforaminal Lumbar Puncture for Intrathecal Nusinersen Administration in Patients with Spinal Muscular Atrophy. AJNR Am J Neuroradiol 42, 980–985 (2021).	Endpoints not fulfilled
47	Gomez Limia, C. et al. Emerging Perspectives on Gene Therapy Delivery for Neurodegenerative and Neuromuscular Disorders. J Pers Med 12, (2022).	Study type not fulfilled
48	Göhl, O. et al. [Respiratory Muscle Training: State of the Art]. Pneumologie 70, 37–48 (2016).	Patient population not fulfilled
49	Giorgia, Q., Gomez Garcia de la, B., a, M. & Smeriglio, P. Role of circulating biomarkers in spinal muscular atrophy: insights from a new treatment era. Front Neurol 14, 1226969 (2023).	Study type not fulfilled
50	Finsterer, J. & Soraru, G. Onset Manifestations of Spinal and Bulbar Muscular Atrophy (Kennedy's Disease). J Mol Neurosci 58, 321–9 (2016).	Endpoints not fulfilled
51	Finsterer, J., Mishra, A., Wakil, S., Pennuto, M. & Soraru, G. Mitochondrial implications in bulbospinal muscular atrophy (Kennedy disease). Amyotroph Lateral Scler Frontotemporal Degener 17, 112–8 (2015).	Study type not fulfilled
52	Finsterer, J. & Aliyev, R. Fasciculations in human hereditary disease. Acta Neurol Belg 115, 91–5 (2015).	Endpoints not fulfilled

53	Landfeldt, E. et al. Caregiver Burden of Spinal Muscular Atrophy: A Systematic Review. Pharmacoeconomics 41, 275–293 (2023).	Endpoints not fulfilled
54	Farrar, M. A. et al. Gene therapy-based strategies for spinal muscular atrophy-an Asia-Pacific perspective. Mol Cell Pediatr 10, 17 (2023).	Study type not fulfilled
55	Facey, K. M. et al. Implementing Outcomes-Based Managed Entry Agreements for Rare Disease Treatments: Nusinersen and Tisagenlecleucel. Pharmacoeconomics 39, 1021–1044 (2021).	Study type not fulfilled
56	Elshafay, A. et al. Efficacy and Safety of Valproic Acid for Spinal Muscular Atrophy: A Systematic Review and Meta-Analysis. CNS Drugs 33, 239–250 (2019).	Endpoints not fulfilled
57	Dunaway Young, S. et al. Six-minute walk test is reliable and valid in spinal muscular atrophy. Muscle Nerve 54, 836–842 (2016).	Study type not fulfilled
58	Dial, A. G., Ng, S. Y., Manta, A. & Ljubicic, V. The Role of AMPK in Neuromuscular Biology and Disease. Trends Endocrinol Metab 29, 300–312 (2018).	Study type not fulfilled
59	Chilcott, E. M., Muiruri, E. W., Hirst, T. C. & Yáñez-Muñoz, R. J. Correction: Systematic review and meta-analysis determining the benefits of in vivo genetic therapy in spinal muscular atrophy rodent models. Gene Ther 30, 188 (2023).	Study type not fulfilled
60	Chilcott, E. M., Muiruri, E. W., Hirst, T. C. & Yáñez-Muñoz, R. J. Systematic review and meta-analysis determining the benefits of in vivo genetic therapy in spinal muscular atrophy rodent models. Gene Ther 29, 498–512 (2022).	Endpoints not fulfilled
61	Cariati, I. et al. Role of Physical Activity in Bone-Muscle Crosstalk: Biological Aspects and Clinical Implications. J Funct Morphol Kinesiol 6, (2021).	Study type not fulfilled
62	Calder, A. N., Androphy, E. J. & Hodgetts, K. J. Small Molecules in Development for the Treatment of Spinal Muscular Atrophy. J Med Chem 59, 10067–10083 (2016).	Study type not fulfilled
63	Butchbach, M. E. Copy Number Variations in the Survival Motor Neuron Genes: Implications for Spinal Muscular Atrophy and Other Neurodegenerative Diseases. Front Mol Biosci 3, 7 (2016).	Endpoints not fulfilled
64	Bray, N., Spencer, L. H. & Edwards, R. T. Preference-based measures of health-related quality of life in congenital mobility impairment: a systematic review of validity and responsiveness. Health Econ Rev 10, 9 (2020).	Endpoints not fulfilled
65	Br, t, M., Johannsen, L., Inhestern, L. & Bergelt, C. Parents as informal caregivers of children and adolescents with spinal muscular atrophy: a systematic review of quantitative and qualitative data on the psychosocial situation, caregiver burden, and family needs. Orphanet J Rare Dis 17, 274 (2022).	Endpoints not fulfilled
66	Bowerman, M. et al. Therapeutic strategies for spinal muscular atrophy: SMN and beyond. Dis Model Mech 10, 943–954 (2017).	Study type not fulfilled

67	Boardman, F. K., Young, P. J. & Griffiths, F. E. Impairment Experiences, Identity and Attitudes Towards Genetic Screening: the Views of People with Spinal Muscular Atrophy. J Genet Couns 27, 69–84 (2018).	Endpoints not fulfilled
68	Bharucha-Goebel, D. & Kaufmann, P. Treatment Advances in Spinal Muscular Atrophy. Curr Neurol Neurosci Rep 17, 91 (2017).	Study type not fulfilled
69	Bernardes Neto, S. C. G., Torres, R., Lima, Í., Resqueti, V. R. & Fregonezi, G. A. F. Weaning from mechanical ventilation in people with neuromuscular disease: protocol for a systematic review. BMJ Open 9, e029890 (2019).	Endpoints not fulfilled
70	Azadinia, F. et al. Can lumbosacral orthoses cause trunk muscle weakness? A systematic review of literature. Spine J 17, 589–602 (2017).	Patient population not fulfilled
71	Arakas, M. R. et al. Functional outcome measures for infantile Charcot-Marie-Tooth disease: a systematic review. J Peripher Nerv Syst 23, 99–107 (2018).	Endpoints not fulfilled
72	Aponte Ribero, V. et al. Systematic Literature Review of the Natural History of Spinal Muscular Atrophy: Motor Function, Scoliosis, and Contractures. Neurology 101, e2103–e2113 (2023).	Endpoints not fulfilled
73	Antonaci, L., Pera, M. C. & Mercuri, E. New therapies for spinal muscular atrophy: where we stand and what is next. Eur J Pediatr 182, 2935–2942 (2023).	Study type not fulfilled
74	Ahmadian-Moghadam, H., Sadat-Shirazi, M. S. & Zarrindast, M. R. Therapeutic potential of stem cells for treatment of neurodegenerative diseases. Biotechnol Lett 42, 1073–1101 (2020).	Study type not fulfilled
75	Abati, E. & Corti, S. Pregnancy outcomes in women with spinal muscular atrophy: A review. J Neurol Sci 388, 50–60 (2018).	Patient population not fulfilled
76	Global, regional, and national burden of motor neuron diseases 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 17, 1083–1097 (2018).	Study type not fulfilled
77	Carrier Screening Programs for Cystic Fibrosis, Fragile X Syndrome, Hemoglobinopathies and Thalassemia, and Spinal Muscular Atrophy: A Health Technology Assessment. Ont Health Technol Assess Ser 23, 1–398 (2023).	Study type not fulfilled
78	Ruta, F., Bassola, B. & Lusignani, M. The characteristics of self-care in children with spinal muscular atrophy: an integrative review. Minerva Pediatr (Torino) 74, 349–357 (2022).	Endpoints not fulfilled
79	Pascual-Morena, C. et al. Onasemnogene Abeparvovec in Type 1 Spinal Muscular Atrophy: A Systematic Review and Meta-Analysis. Hum Gene Ther 34, 129–138 (2023).	Patient population not fulfilled
80	Duan, D. Lethal immunotoxicity in high-dose systemic AAV therapy. Mol Ther 31, 3123–3126 (2023).	Endpoints not fulfilled

81	Chiriboga, C. A. Nusinersen for the treatment of spinal muscular atrophy. Expert Rev Neurother 17, 955–962 (2017).	Endpoints not fulfilled
82	Castro-Codesal, M. L. et al. Long-term non-invasive ventilation therapies in children: A scoping review. Sleep Med Rev 37, 148–158 (2018).	Study type not fulfilled
83	Chen, D., Ni, J. & Buu, M. Genetic therapies and respiratory outcomes in patients with neuromuscular disease. Curr Opin Pediatr 36, 296–303 (2024).	Study type not fulfilled
84	Ahmady, A. et al. Comparison of Distal Spine Anchors and Distal Pelvic Anchors in Children With Hypotonic Neuromuscular Scoliosis Treated With Growth-friendly Instrumentation. J Pediatr Orthop 43, e319–e325 (2023).	Patient population not fulfilled
85	Boentert, M., Wenninger, S. & Sansone, V. A. Respiratory involvement in neuromuscular disorders. Curr Opin Neurol 30, 529–537 (2017).	Study type not fulfilled

Table 5: List of included systematic reviews and meta-analyses

No	Study title
1	Abbas, K. S., Eltaras, M. M., El-Shahat, N. A., Abdelazeem, B., Shaqfeh, M., & Brašić, J. R. (2022). The Safety and Efficacy of Nusinersen in the Treatment of Spinal Muscular Atrophy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Medicina (Kaunas), 58(2). https://doi.org/10.3390/medicina58020213
2	AlBalawi, M. M., Castro-Codesal, M., Featherstone, R., Sebastianski, M., ermeer, B., Alkhaledi, B., Bedi, P. K., Abusido, T., & MacLean, J. E. (2022). Outcomes of Long-Term Noninvasive Ventilation Use in Children with Neuromuscular Disease: Systematic Review and Meta-Analysis. Ann Am Thorac Soc, 19(1), 109–119. https://doi.org/10.1513/AnnalsATS.202009-1089OC
3	Albrechtsen, S. S., Born, A. P., & Boesen, M. S. (2020). Nusinersen treatment of spinal muscular atrophy - a systematic review. Dan Med J, 67(9).
4	Alhammoud, A., Othman, Y., El-Hawary, R., Mackenzie, W. G., & Howard, J. J. (2021). The impact of scoliosis surgery on pulmonary function in spinal muscular atrophy: a systematic review. Spine Deform, 9(4), 913–921. https://doi.org/10.1007/s43390-021-00302-w
5	Al-Taie, A., & Köseoğlu, A. (2023). Evaluation of the therapeutic efficacy and tolerability of current drug treatments on the clinical outcomes of paediatric spinal muscular atrophy type 1: A systematic review. Paediatr Respir Rev, 48, 65–71. https://doi.org/10.1016/j.prrv.2023.06.004
6	Angeli, M., Alpantaki, K., is, N., Koutserimpas, C., & Hadjipavlou, A. (2022). The effect of scoliosis surgery on pulmonary function in spinal muscular atrophy patients: review of the literature and a meta-analysis. Eur Spine J, 31(9), 2279–2286. https://doi.org/10.1007/s00586-022-07182-2
7	Aragon-Gawinska, K., Mouraux, C., Dangouloff, T., & Servais, L. (2023). Spinal Muscular Atrophy Treatment in Patients Identified by Newborn Screening-A Systematic Review. Genes (Basel), 14(7). https://doi.org/10.3390/genes14071377

8	Baranello, G., Gorni, K., Daigl, M., Kotzeva, A., Evans, R., Hawkins, N., Scott, D. A., Mahajan, A., Muntoni, F., & Servais, L. (2021). Prognostic Factors and Treatment-Effect Modifiers in Spinal Muscular Atrophy. Clin Pharmacol Ther, 110(6), 1435–1454. https://doi.org/10.1002/cpt.2247
9	Bedi, P. K., Castro-Codesal, M. L., Featherstone, R., AlBalawi, M. M., Alkhaledi, B., Kozyrskyj, A. L., Flores-Mir, C., & MacLean, J. E. (2018). Long-term Non-Invasive Ventilation in Infants: A Systematic Review and Meta-Analysis. Front Pediatr, 6, 13. https://doi.org/10.3389/fped.2018.00013
10	Bellai, D. J., & Rae, M. G. (2024). A systematic review of the association between the age of onset of spinal bulbar muscular atrophy (Kennedy's disease) and the length of CAG repeats in the androgen receptor gene. ENeurologicalSci, 34, 100495. https://doi.org/10.1016/j.ensci.2024.100495
11	Bischof, M., Lorenzi, M., Lee, J., Druyts, E., Balijepalli, C., & Dabbous, O. (2021). Matching-adjusted indirect treatment comparison of onasemnogene abeparvovec and nusinersen for the treatment of symptomatic patients with spinal muscular atrophy type 1. Curr Med Res Opin, 37(10), 1719–1730. https://doi.org/10.1080/03007995.2021.1947216
12	Claborn, M. K., Stevens, D. L., Walker, C. K., & Gildon, B. L. (2019). Nusinersen: A Treatment for Spinal Muscular Atrophy. Ann Pharmacother, 53(1), 61–69. https://doi.org/10.1177/1060028018789956
13	Cobo-Vicente, F., San Juan, A. F., Larumbe-Zabala, E., Estévez-González, A. J., Donadio, M. V. F., & Pérez-Ruiz, M. (2021). Neuromuscular Electrical Stimulation Improves Muscle Strength, Biomechanics of Movement, and Functional Mobility in Children With Chronic Neurological Disorders: A Systematic Review and Meta-Analysis. Phys Ther, 101(10). https://doi.org/10.1093/ptj/pzab170
14	Coratti, G., Cutrona, C., Pera, M. C., Bovis, F., Ponzano, M., Chieppa, F., Antonaci, L., Sansone, V., Finkel, R., Pane, M., & Mercuri, E. (2021). Motor function in type 2 and 3 SMA patients treated with Nusinersen: a critical review and meta-analysis. Orphanet J Rare Dis, 16(1), 430. https://doi.org/10.1186/s13023-021-02065-z
15	Dosi, C., & Masson, R. (2024). The impact of three SMN2 gene copies on clinical characteristics and effect of disease-modifying treatment in patients with spinal muscular atrophy: a systematic literature review. Front Neurol, 15, 1308296. https://doi.org/10.3389/fneur.2024.1308296
16	Erdos, J., & Wild, C. (2022). Mid- and long-term (at least 12 months) follow-up of patients with spinal muscular atrophy (SMA) treated with nusinersen, onasemnogene abeparvovec, risdiplam or combination therapies: A systematic review of real-world study data. Eur J Paediatr Neurol, 39, 1–10. https://doi.org/10.1016/j.ejpn.2022.04.006
17	Gavriilaki, M., Moschou, M., Papaliagkas, V., Notas, K., Chatzikyriakou, E., Papagiannopoulos, S., Arnaoutoglou, M., & Kimiskidis, V. K. (2022). Nusinersen in Adults with 5q Spinal Muscular Atrophy: a Systematic Review and Meta-analysis. Neurotherapeutics, 19(2), 464–475. https://doi.org/10.1007/s13311-022-01200-3
18	Gavriilaki, M., Moschou, M., Papaliagkas, V., Notas, K., Chatzikyriakou, E., Zafeiridou, G., Papagiannopoulos, S., Arnaoutoglou, M., & Kimiskidis, V. K. (2022). Biomarkers of disease progression in adolescents and adults with 5q spinal muscular atrophy: a systematic review and meta-analysis. Neuromuscul Disord, 32(3), 185–194. https://doi.org/10.1016/j.nmd.2021.12.005
19	Gavriilaki, M., Papaliagkas, V., Stamperna, A., Moschou, M., Notas, K., Papagiannopoulos, S., Arnaoutoglou, M., & Kimiskidis, V. K. (2023). Biomarkers of therapeutic efficacy in adolescents and adults with 5q spinal muscular atrophy: a systematic review. Acta Neurol Belg, 123(5), 1735–1745. https://doi.org/10.1007/s13760-022-02028-6

20	Jiang, T., Youn, B., Paradis, A. D., Beckerman, R., Barnieh, L., & Johnson, N. B. (2023). A Critical Appraisal of Matching-Adjusted Indirect Comparisons in Spinal Muscular Atrophy. Adv Ther, 40(7), 2985–3005. https://doi.org/10.1007/s12325-023-02520-2
21	Kennedy, R. A., Carroll, K., McGinley, J. L., & Paterson, K. L. (2020). Walking and weakness in children: a narrative review of gait and functional ambulation in paediatric neuromuscular disease. J Foot Ankle Res, 13(1), 10. https://doi.org/10.1186/s13047-020-0378-2
22	Landfeldt, E., Edström, J., Sejersen, T., Tulinius, M., Lochmueller, H., & Kirschner, J. (2019). Quality of life of patients with spinal muscular atrophy: a systematic review. European Journal of Paediatric Neurology, 23(3), 347–356.
23	Lin, C. W., Kalb, S. J., & Yeh, W. S. (2015). Delay in Diagnosis of Spinal Muscular Atrophy: A Systematic Literature Review. Pediatr Neurol, 53(4), 293–300. https://doi.org/10.1016/j.pediatrneurol.2015.06.002
24	Mercuri, E., Lucibello, S., Perulli, M., Coratti, G., de Sanctis, R., Pera, M. C., Pane, M., Montes, J., de Vivo, D. C., Darras, B. T., Kolb, S. J., & Finkel, R. S. (2020). Longitudinal natural history of type I spinal muscular atrophy: a critical review. Orphanet J Rare Dis, 15(1), 84. https://doi.org/10.1186/s13023-020-01356-1
25	Meylemans, A., & De Bleecker, J. (2019). Current evidence for treatment with nusinersen for spinal muscular atrophy: a systematic review. Acta Neurol Belg, 119(4), 523–533. https://doi.org/10.1007/s13760-019-01199-z
26	Moore, G. E., Lindenmayer, A. W., McConchie, G. A., Ryan, M. M., & Davidson, Z. E. (2016). Describing nutrition in spinal muscular atrophy: A systematic review. Neuromuscul Disord, 26(7), 395–404. https://doi.org/10.1016/j.nmd.2016.05.005
27	Pascual-Morena, C., Martínez-Vizcaíno, V., Cavero-Redondo, I., Martínez-García, I., Moreno-Herráiz, N., Álvarez-Bueno, C., & Saz-Lara, A. (2024). Efficacy of risdiplam in spinal muscular atrophy: A systematic review and meta-analysis. Pharmacotherapy, 44(1), 97–105. https://doi.org/10.1002/phar.2866
28	Polido, G. J., de, M., a, M. M. V, Carvas, N., Mendonça, R. H., Caromano, F. A., Reed, U. C., Zanoteli, E., & Voos, M. C. (2019). Cognitive performance of children with spinal muscular atrophy: A systematic review. Dement Neuropsychol, 13(4), 436–443. https://doi.org/10.1590/1980-57642018dn13-040011
29	Qiao, Y., Chi, Y., Gu, J., & Ma, Y. (2023). Safety and Efficacy of Nusinersen and Risdiplam for Spinal Muscular Atrophy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Brain Sci, 13(10). https://doi.org/10.3390/brainsci13101419
30	Ribero, V. A., Daigl, M., Martí, Y., Gorni, K., Evans, R., Scott, D. A., Mahajan, A., Abrams, K. R., & Hawkins, N. (2022). How does risdiplam compare with other treatments for Types 1-3 spinal muscular atrophy: a systematic literature review and indirect treatment comparison. J Comp Eff Res, 11(5), 347–370. https://doi.org/10.2217/cer-2021-0216
31	Stevens, D., Claborn, M. K., Gildon, B. L., Kessler, T. L., & Walker, C. (2020). Onasemnogene Abeparvovecxioi: Gene Therapy for Spinal Muscular Atrophy. Ann Pharmacother, 54(10), 1001–1009. https://doi.org/10.1177/1060028020914274
32	Wadman, R. I., van der Pol, W. L., Bosboom, W. M. J., Asselman, F. L., van den Berg, L. H., Iannaccone, S. T., & Vrancken, A. (2020). Drug treatment for spinal muscular atrophy types II and III. Cochrane Database of Systematic Reviews, 1. https://doi.org/10.1002/14651858.CD006282.pub5
33	Wadman, R. I., van der Pol, W. L., Bosboom, W. M. J., Asselman, F., van den Berg, L. H., Iannaccone, S. T., & Vrancken, A. F. J. E. (2019). Drug treatment for spinal muscular atrophy type I. Cochrane Database of Systematic Reviews, 12.

34	Wan, H. W. Y., Carey, K. A., D'Silva, A., Vucic, S., Kiernan, M. C., Kasparian, N. A., & Farrar, M. A. (2020). Health, wellbeing and lived experiences of adults with SMA: a scoping systematic review. Orphanet J Rare Dis, 15(1), 70. https://doi.org/10.1186/s13023-020-1339-3
35	Wijngaarde, C. A., Blank, A. C., Stam, M., Wadman, R. I., van den Berg, L. H., & van der Pol, W. L. (2017). Cardiac pathology in spinal muscular atrophy: a systematic review. Orphanet J Rare Dis, 12(1), 67. https://doi.org/10.1186/s13023-017-0613-5
36	Wu, J. W., Pepler, L., Maturi, B., Afonso, A. C. F., Sarmiento, J., & Haldenby, R. (2022). Systematic Review of Motor Function Scales and Patient-Reported Outcomes in Spinal Muscular Atrophy. Am J Phys Med Rehabil, 101(6), 590–608. https://doi.org/10.1097/phm.0000000000001869
37	Yang, D., Ruan, Y., & Chen, Y. (2023). Safety and efficacy of gene therapy with onasemnogene abeparvovec in the treatment of spinal muscular atrophy: A systematic review and meta-analysis. J Paediatr Child Health, 59(3), 431–438. https://doi.org/10.1111/jpc.16340
38	Yang, M., Awano, H., Tanaka, S., Toro, W., Zhang, S., Dabbous, O., & Igarashi, A. (2022). Systematic Literature Review of Clinical and Economic Evidence for Spinal Muscular Atrophy. Advances in Therapy, 39(5), 1915–1958. https://doi.org/10.1007/S12325-022-02089-2
39	Zhong, Z. J., Zheng, P. M., Dou, H. H., & Wang, J. G. (2023). Adverse events in the treatment of spinal muscular atrophy in children and adolescents with nusinersen: A systematic review and meta-analysis. Front Pediatr, 11, 1152318. https://doi.org/10.3389/fped.2023.1152318

3.2 Overview of Identified Confounders

We conducted a comprehensive literature review to systematically identify evidence-based guidelines, recommendations, systematic reviews, and meta-analyses that report potential confounders in the context of SMA. This review involved extensive literature searching in relevant databases. The inclusion criteria encompass pre-symptomatic patients with 5q-associated SMA having a biallelic mutation in the SMN1 gene and up to three copies of the SMN2 gene, as well as symptomatic patients categorized by SMA type. The tables detail the confounders and prognostic factors identified from the literature, with the importance of each confounder identified by key opinion leaders provided in the following tables.

The review identified several critical confounders influencing outcomes in SMA patients. The age of onset is a significant factor for symptomatic patients (types I, II, and III), with earlier onset often correlating with more severe disease progression, and is of less importance according to key opinion leaders. Age at treatment initiation is crucial across all patient types, impacting disease progression and quality of life, and is considered very important. Comorbidities, while relevant for all patient types, are deemed not important. Regional and cultural standards influence access to care and treatment efficacy for all patient types but are not important.

Lean body mass and race are notable for specific SMA types but are not important. Understanding the origin of SMA disease is crucial. Differentiating between different SMA types is essential for tailoring treatment plans and understanding disease severity, though this is considered not important. The number of SMN2 gene copies is very important for all patient categories, influencing disease severity and treatment response. Genotype variants, however, are not important.

Treatment response is another vital aspect. Initiating treatment in pre-symptomatic stages can significantly improve outcomes across all patient types and is very important. Early diagnosis and genetic screening are essential for timely treatment initiation, which is crucial for better outcomes but is considered not important. Nutritional manifestations play a significant role in managing SMA. Gastrostomy and nutritional support are important for symptomatic patients but are considered not important. Issues such as feeding and swallowing difficulties are less important. Bone mineral density issues are not important. Orthopedic and motoric manifestations are also critical. Contractures and motoric function significantly affect mobility and quality of life in symptomatic patients, with contractures being less important and motoric function being very important. Various functional scores, such as the Hammersmith Motor Function Scale Expanded (HFMSE), are very important for evaluating motor function and tracking disease progression. Respiratory function management, including ventilatory support, is very important for maintaining overall health, while other aspects like airway secretion clearance and lung function are less important.

Other factors include pain management and family support, which are vital for the patient's quality of life and well-being but are not important. The response to treatments and genetic factors influence treatment efficacy and disease progression but are not important. Additionally, multiple disorders and complications can complicate treatment and affect prognosis, with complications being not important. Biomarkers are valuable for monitoring disease progression and response to treatment but are not important.

3.3 Phase 2: Validation of Confounders

Phase 2 of the project focused on verifying the relevance of confounders identified from national and international guidelines, systematic reviews, and meta-analyses related to SMA. This phase began with extracting potentially relevant confounders from the literature and evaluating their impact on the target population.

We conducted a workshop with 7 clinical experts on 4th June 2024, presenting the identified confounders to the panel for ranking. The methodology involved interviews and workshops with key opinion leaders (KOLs) from the SMA field to discuss and evaluate each confounder’s relevance and potential impact on SMA research, particularly to aid Roche in analyzing data for Evrysdi (risdiplam) benefit assessments in Germany.

Feedback from these discussions was analyzed to identify the most significant and relevant confounders. These were categorized into three groups:

Very Important: Essential for adjusting non-randomized studies to ensure validity.

Less Important: Marginally affect outcomes but not critical to study validity.

Not Important: Irrelevant to the study due to specific characteristics.

The outcomes are provided in the following tables.

Table 6: Confounders at baseline - Category patient characteristics

Confounder/ Prognostic Factor	Characteristics	Relevance for					Importance for Study (Key Opinion Leaders)	Sources
		Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III		
Age onset	Age at symptom onset	NA	NA	✓	✓	✓	Less important	(NICE, 2016), (Claborn et al., 2019), (Wan et al., 2020), (Albrechtsen et al., 2020), (Polido et al., 2019), (Amin et al., 2017), (Baranello et al., 2021), (Bischof et al., 2021), (Cobo-Vicente et al., 2021), (Kennedy et al., 2020), (Abbas et al., 2022), (Angeli et al., 2022), (Gavriilaki et al., 2022), (Ribero et al., 2022), (Wu et al., 2022), (M. Yang et al., 2022), (Zhong et al., 2023), (Qiao et al., 2023), (Al-Taie & Köseoğlu, 2023), (Gavriilaki et al., 2023), (D. Yang et al., 2023), (Bellai & Rae, 2024), (Dosi & Masson, 2024), (Mercuri et al., 2020), (Lin et al., 2015), (Wadman et al., 2019), (Ziegler et al., 2020), (Mercuri et al., 2018), (Dryden Palmer et al., 2022), (Nennstiel et al., 2020)
Age Treatment initiation	Age at treatment	✓	✓	✓	✓	✓	Very important	(Stevens et al., 2020), (Albrechtsen et al., 2020), (Solé et al., 2020), (Alhammoud et al., 2021), (Baranello et al., 2021), (Bischof et al., 2021), (Jiang et al., 2023), (D. Yang et al., 2023), (Aragon-Gawinska et al., 2023), (Pascual-Morena et al., 2024), (Michelson et al., 2018), (Kichula et al., 2021), (Dryden Palmer et al., 2022)
	Age at study start (first dose)	NA	NA	✓	✓	✓	Very important	(Mercuri et al., 2020)
	Early treatment initiation	NA	NA	✓	✓	✓	Very important	(Wan et al., 2020), (Wadman et al., 2019), (Erdos & Wild, 2022)

Comorbidities	Comorbidities	✓	✓	✓	✓	✓	Not important	(Wan et al., 2020), (Mercuri et al., 2020)
Region	Regional and cultural standards	✓	✓	✓	✓	✓	Not important	(Lin et al., 2015), (Mercuri et al., 2018)
Lean body mass		NA	NA	✓	✓	NA	Not important	(C. H. Wang et al., 2007)
Race		NA	NA		✓	NA	Not important	(Prior, 2008)

Abbreviations: SMA: Spinal Muscular Atrophy.

Table 7: Confounders at baseline - category origin of SMA disease

Confounder/ Prognostic Factor	Characteristics	Relevance for					Importance for Study	Sources
		Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III		
SMA Type	SMA Type	NA	NA	✓	✓	✓	Not important: (Age at onset & highest motor milestone at baseline captured individually)	(Lin et al., 2015), (Stevens et al., 2020), (Albrechtsen et al., 2020), (Polido et al., 2019), (Wijngaarde et al., 2017), (Amin et al., 2017), (Bedi et al., 2018), (Landfeldt et al., 2019), (Alhammoud et al., 2021), (Coratti et al., 2021), (Angeli et al., 2022), (Erdos & Wild, 2022), (Gavriilaki et al., 2022), (Ribero et al., 2022), (Gavriilaki et al., 2023), (D. Yang et al., 2023), (Kichula et al., 2021), (Ziegler et al., 2020), (Nennstiel et al., 2020)
SMN2 copy number	SMN2 copy number	✓	✓	✓	✓	✓	Very important	(Claborn et al., 2019), (Stevens et al., 2020), (Wadman et al., 2019), (Mercuri et al., 2020), (Wadman et al., 2020), (Cuscó et al., 2020), (Glascock et al., 2020), (Wijngaarde et al., 2017), (Baranello et al., 2021), (Bischof et al., 2021), (Cobo-Vicente et

								al., 2021), (Abbas et al., 2022), (Gavriilaki et al., 2022), (Erdos & Wild, 2022), (Ribero et al., 2022), (Wu et al., 2022), (M. Yang et al., 2022), (Al-Taie & Köseoğlu, 2023), (Aragon-Gawinska et al., 2023), (Gavriilaki et al., 2023), (Jiang et al., 2023), (Qiao et al., 2023), (D. Yang et al., 2023), (Zhong et al., 2023), (Dosi & Masson, 2024), (Pascual-Morena et al., 2024), (Pitarch Castellano et al., 2022), (Abiusi et al., 2023), (Kichula et al., 2021), (Dryden Palmer et al., 2022),(Cuscó et al., 2024), (Nennstiel et al., 2020)
SMN2 genotype/variants	Genotype of SMN2	✓	✓	✓	✓	✓	Not important	(Glascock et al., 2020), (Meylemans & De Bleecker, 2019), (Michelson et al., 2018), (Polido et al., 2019), (Angeli et al., 2022),(Lee et al., 2021), (Ziegler et al., 2020), (Mercuri et al., 2018), (Cuscó et al., 2024)

Abbreviations: SMA: Spinal Muscular Atrophy.

Table 8: Confounders at baseline - category impact on the treatment response

Confounder/Prognostic Factor	Characteristics	Relevance for					Importance for Study	Sources
		Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III		
Pre-symptomatic/ symptomatic at treatment initiation	Pre-symptomatic/ symptomatic at treatment initiation	✓	✓	✓	✓	✓	Very important	(Wan et al., 2020), (Lee et al., 2021), (Cuscó et al., 2024), (Nennstiel et al., 2020)

Early diagnosis	Time between diagnosis or symptom onset and start of treatment	✓	✓	✓	✓	✓	Not important	(Lin et al., 2015), (NICE, 2016), (Oliver et al., 2017), (Milligan et al., 2022), (Nennstiel et al., 2020)
	Neonatal Screening and Early Diagnosis	✓	✓	✓	✓	✓	Very important	(Albrechtsen et al., 2020), (Abiusi et al., 2023), (Cuscó et al., 2024)

Abbreviations: SMA: Spinal Muscular Atrophy.

Table 9: Confounders at baseline - category nutrition manifestations

Confounder/ Prognostic Factor	Characteristics	Relevance for					Importance for Study	Sources
		Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III		
Gastrostomy	Gastroesophageal reflux	✓	✓	✓	✓		Not important	(C. H. Wang et al., 2007)
	Gastrostomy tube feeding	NA	NA	✓	✓	✓	Not important	(Polido et al., 2019), (Moore et al., 2016), (NICE, 2016)
	Gastrostomy placement	NA	NA	✓	✓	✓	Not important	(Amin et al., 2017)
Nutrition	Nutritional support	NA	NA	✓	✓	✓	Very important	(Amin et al., 2017), (Bischof et al., 2021), (Erdos & Wild, 2022), (Al-Taie & Köseoğlu, 2023), (Aragon-Gawinska et al., 2023), (Jiang et al., 2023), (Zhong et al., 2023), (Kichula et al., 2021), (Ziegler et al., 2020), (Finkel et al., 2018)

	Over/under-nutrition	✓	✓	✓	✓	✓	Not important	(Moore et al., 2016)
	Feeding and Swallowing Issues	NA	NA	✓	✓	✓	Less important	(Moore et al., 2016), (Cobo-Vicente et al., 2021), (Lee et al., 2021)
	Bone mineral density	NA	NA	✓	✓	✓	Not important	(Cobo-Vicente et al., 2021)

Abbreviations: SMA: Spinal Muscular Atrophy.

Table 10: Confounders at baseline - category orthopaedic and motoric manifestations

Confounder/ Prognostic Factor	Characteristics	Relevance for					Importance for Study	Sources
		Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III		
Contractures	Contractures	NA	NA	✓	✓	✓	Less important	(Mercuri et al., 2020)
	Flexion Contractures	✓	✓	✓	✓	NA	Less important	(C. H. Wang et al., 2007)

Motoric function	Highest motor milestone at baseline	NA	NA	NA	✓	✓	Very important	(Claborn et al., 2019), (Mercuri et al., 2020), (Wadman et al., 2020), (Landfeldt et al., 2019), (Kennedy et al., 2020), (Abbas et al., 2022), (Gavriilaki, Moschou, Papaliagkas, Notas, Chatzikyriakou, Zafeiridou, et al., 2022), (Gavriilaki, Moschou, Papaliagkas, Notas, Chatzikyriakou, Papagiannopoulos, et al., 2022), (Ribero et al., 2022), (Wu et al., 2022), (M. Yang et al., 2022), (D. Yang et al., 2023), (Zhong et al., 2023), (Bellai & Rae, 2024), (Pascual-Morena et al., 2024), (Pitarch Castellano et al., 2022), (Ziegler et al., 2020), (Dryden Palmer et al., 2022), (Finkel et al., 2018)
	HFMSE score, 6MWT, ADL Scores	NA	NA	✓	✓	✓	Very important	(Wan et al., 2020), (Meylemans & De Bleecker, 2019), (Coratti et al., 2021), (Gavriilaki, Moschou, Papaliagkas, Notas, Chatzikyriakou, Zafeiridou, et al., 2022), (Jiang et al., 2023), (Qiao et al., 2023), (Dosi & Masson, 2024), (Pascual-Morena et al., 2024)
	RULM score	NA	NA	✓	✓	✓	Very important	(Wan et al., 2020), (Gavriilaki, Moschou, Papaliagkas, Notas, Chatzikyriakou, Zafeiridou, et al., 2022)(Jiang et al., 2023), (Qiao et al., 2023)
	HINE-2 score	NA	NA	✓	✓	✓	Very important	
	CHOP-INTEND score	✓	✓	✓	✓	✓	Very important	(Mercuri et al., 2020), (Stevens et al., 2020), (Wadman et al., 2019), (Bischof et al., 2021), (Lee et al., 2021)
Physical activity	Physical activity	NA	NA	✓	✓	✓	Not important	(Wan et al., 2020)
	Physiotherapy	NA	NA	✓	✓	NA	Less important	(C. H. Wang et al., 2007)
Orthotics		NA	NA	✓	✓	NA	Not important	(C. H. Wang et al., 2007)

Abbreviations: 6MWT: 6-Minute Walk Test, ADL: Activities of Daily Living, CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, HFMSE: Hammersmith Functional Motor Scale Expanded, HINE: Hammersmith Infant Neurological Exam, RULM: Revised Upper Limb Module, SMA: Spinal Muscular Atrophy.

Table 11: Confounders after baseline – category respiratory function

Confounder/ Prognostic Factor	Characteristics	Relevance for					Importance for Study	Sources
		Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III		
Respiratory function	FVC measure	NA	NA	✓	✓	✓	Less important	(Wadman et al., 2019), (Wadman et al., 2020), (AlBalawi et al., 2022), (Zhong et al., 2023), (Pascual-Morena et al., 2024), (NICE, 2016), (Oliver et al., 2017), (Nennstiel et al., 2020)
	Ventilatory Support	NA	NA	✓	✓	✓	Very important	(Amin et al., 2017), (Al-Taie & Köseoğlu, 2023), (Jiang et al., 2023) (Claborn et al., 2019), (Albrechtsen et al., 2020), (Aragon-Gawinska et al., 2023), (Lee et al., 2021), (Kichula et al., 2021), (Ziegler et al., 2020)
	Airway secretion clearance	NA	NA	✓	✓	✓	Less important	(Angeli et al., 2022)
	Lung function	✓	✓	✓	✓	✓	Less important	(Gavriilaki, Moschou, Papaliagkas, Notas, Chatzikyriakou, Zafeiridou, et al., 2022), (Finkel et al., 2018)

Abbreviations: FVC: Forced Vital Capacity, SMA: Spinal Muscular Atrophy.

Table 12: Confounders after baseline – category others

Confounder/ Prognostic Factor	Characteristics	Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	Importance for Study	Sources
Pain management	Pain management	NA	NA	✓	✓	✓	Not important	(Wan et al., 2020)
Support	Support from family	✓	✓	✓	✓	✓	Not important	(Wan et al., 2020), (Glascock et al., 2020)
Response to Treatments	Response to Treatments	NA	NA	✓	✓	✓	Not important	(Solé et al., 2020)
Genetic factors	Genetic modifiers	✓	✓	✓	✓	✓	Not important	(Claborn et al., 2019), (Stevens et al., 2020), (Wadman et al., 2019), (Baranello et al., 2021), (Aragon-Gawinska et al., 2023), (Lee et al., 2021), (Nennstiel et al., 2020)
	SMN1 Gene Mutations	✓	✓	✓	✓	✓	Not important	(Al-Taie & Köseoğlu, 2023), (Milligan et al., 2022), (Mercuri et al., 2018)
Multiple disorders	Multiple disorders	NA	NA	✓	✓	✓	Less important	(Bedi et al., 2018)
Complications	Complications	✓	✓	✓	✓	✓	Not important	(Alhammoud et al., 2021), (Pitarch Castellano et al., 2022), (Ziegler et al., 2020), (Dryden Palmer et al., 2022)
Biomarkers	Neurophysiologic Biomarkers	NA	NA	✓	✓	✓	Not important	(Dosi & Masson, 2024; Gavriilaki, Moschou, Papaliagkas, Notas, Chatzikyriakou, Papagiannopoulos, et al., 2022), (Lee et al., 2021)

	Other bi-omarkers			✓	✓	✓	Not important	(Dosi & Masson, 2024)
Access/quality	Access/quality	✓	✓	✓	✓	NA	Not important	(C. H. Wang et al., 2007)
Adaptation	Adaptation	NA		✓		NA	Not important	(C. H. Wang et al., 2007)
Nutrition	Education about nutri-tion	✓	✓	✓	✓	NA	Not important	(C. H. Wang et al., 2007)

Table 13: Details of confounders /prognostic factors from included systematic reviews and meta-analysis

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
1	Claborn 2019	Age onset	Age at symptom onset	✓	✓	✓	✓	✓	SMA is classified into types based on the age of onset, which correlates with disease severity. Earlier onset (such as in type 0 and type 1, which occur before 6 months of age) is associated with more severe disease and poorer prognosis. Later onset types (such as Types 2, 3, and 4) present with milder symptoms and a better prognosis.
		SMN2 copy number	SMN2 copy number	✓	✓	✓	✓	✓	The number of copies of the SMN2 gene is a significant prognostic factor. Patients with more copies of SMN2 tend to have a milder form of SMA. For example, individuals with only one copy of SMN2 have a very severe form of the disease and a shortened life expectancy, while those with more copies have less severe symptoms and a longer life expectancy.
		Motoric function	Highest motor milestone at baseline	✓	✓	✓	✓	✓	The maximum motor function attained is another prognostic factor. This includes the ability to sit, stand, or walk. Patients who achieve higher motor milestones generally have a better prognosis.
		Respiratory function	Ventilatory support	✓		✓			The need for respiratory support at birth is indicative of a more severe disease form. Patients requiring such support typically have a worse prognosis.
		Genetic factors	Genetic factors	✓	✓	✓	✓	✓	A homozygous deletion of SMN1 exon 7 is confirmatory for SMA diagnosis. This genetic marker helps in diagnosing the severity of the disease and aids in prognostication.
2	Wan 2020	Age onset	Age at symptom onset	✓	✓	✓	✓	✓	The age of onset plays a significant role in prognosis. Earlier onset (e.g., SMA type IIIa with onset before 3 years of age) is generally

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
									associated with a more rapid decline in function compared to later onset (e.g., SMA type IIIb with onset after 3 years of age).
		Physical activity	Physical activity	✓	✓	✓	✓	✓	The role of physical activity is mentioned with respect to maintaining muscle function and mobility. The paper discusses that engagement in physical activities correlates with slower progression in motor function decline.
		Comorbidities	Comorbidities			✓	✓	✓	The presence of comorbidities can influence the rate of deterioration and overall prognosis. Studies have shown that the rate of decline in muscle strength and function can vary significantly based on the presence of additional health issues.
		Age Treatment initiation	Age at treatment	✓	✓	✓	✓	✓	The age at which treatment is initiated significantly impacts the effectiveness of therapies. For instance, studies have shown that early treatment with disease-modifying therapies can result in significant improvements in motor function and delay the progression of the disease. In contrast, treatment initiated later in life, especially in adults with longstanding SMA, shows more modest improvements due to the advanced stage of motor neuron degeneration.
			Early treatment initiation	✓	✓	✓	✓	✓	The paper emphasizes the importance of early treatment initiation in improving outcomes for individuals with SMA. Early intervention, particularly in the presymptomatic stage, is associated with better motor function and slower disease progression. Nusinersen, when initiated in infants during the presymptomatic stage, has shown interim efficacy and safety results that highlight the benefits of early treatment.

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
		Presymptomatic/ symptomatic at treatment initiation	Presymptomatic/ symptomatic at treatment initiation	✓	✓	✓	✓	✓	The initiation of treatment during the presymptomatic stage is associated with significantly better outcomes. Studies have shown that treatments like nusinersen are more effective when administered early, leading to better motor function and slower disease progression. This highlights the importance of early diagnosis and intervention.
		Motoric function	- HFMSE score	✓	✓	✓	✓	✓	The rate of muscle strength decline is a significant prognostic factor. Studies have shown a mean annual loss of 0.5 point for the HFMSE.
			- RULM score	✓	✓	✓	✓	✓	Declines in motor function measures such as the RULM score is important for predicting disease progression. These measures help in assessing the gradual loss of motor skills over time.
		Pain management	Pain management	✓	✓	✓	✓	✓	The paper does not detail specific strategies for pain management within the sections provided. However, it does discuss the management of physical symptoms and the general approach to supportive care which likely encompasses pain management strategies.
		Support	Support from family			✓	✓	✓	The paper emphasizes the significant role of family support in managing SMA, highlighting how supportive family environments influence both psychological and physical health outcomes. It notes that strong relationships with family and friends are crucial for coping and engaging positively with the disease.
3	Mercuri 2020	Age Treatment initiation	Age at treatment	✓	✓	✓	✓	✓	The paper mentions the availability of treatments like nusinersen and Zolgensma, which have shown positive results, particularly when administered early. This emphasizes that early treatment initiation is crucial for improving motor function and slowing disease
			Age at study start (first dose)	✓	✓	✓	✓	✓	

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
									progression in SMA patients. "The cumulative findings in this review help to better understand the variability of natural history data in untreated patients and will be of use for comparison to the real-world patients treated with the recently approved therapies that have shown encouraging results in clinical trials".
		Comorbidities	Comorbidities	✓	✓	✓	✓	✓	The study notes that the severity of the phenotype, including respiratory and feeding difficulties, influences disease progression and outcomes. Infants with more severe comorbid conditions tend to exhibit faster declines in motor function and overall health. This highlights the critical role of comorbidities in the clinical management and prognostic assessment of SMA. "These studies described for the first time the range of changes, suggesting some variability in the results that were possibly related to a number of factors, including baseline values, age, duration of symptoms, and the severity of the phenotype with associated respiratory and feeding comorbidities progression".
		Contractures	Contractures	✓	✓	✓	✓	✓	In infants with type I SMA, which is the most severe form of the disease, the loss of motor neurons leads to profound muscle weakness and atrophy. As the muscles weaken and are used less frequently, they may shorten, leading to contractures. These typically occur in the limbs, and can severely restrict joint mobility.
		SMN2 Copy Number	SMN2 Copy Number	✓	✓	✓	✓	✓	The number of SMN2 gene copies is a critical prognostic factor for SMA. The study found that patients with fewer SMN2 copies, particularly those with two copies, exhibited a more severe disease progression and faster decline in motor function. In contrast,

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
									patients with three or more SMN2 copies showed a slower rate of decline. For instance, the paper notes that patients with two SMN2 copies had varied rates of progression based on their baseline CHOP-INTEND scores, while the unique patient with four copies had a significantly slower rate of progression. These findings underscore the importance of SMN2 copy number in determining the clinical trajectory of SMA patients.
		Motoric function	CHOP-INTEND scores	✓	✓	✓	✓	✓	Baseline CHOP-INTEND scores are a significant predictor of disease progression in SMA patients. The study categorizes patients based on their initial CHOP-INTEND scores and finds that those with lower scores at baseline (below 25) tend to experience a faster decline in motor function. Specifically, patients with scores between 25 and 35 also show a rapid decline, while those with scores above 35 experience a slower progression. This variability in progression rates is crucial for understanding individual patient trajectories and highlights the prognostic value of initial CHOP-INTEND assessment.
		Age onset	Age at symptom onset	✓	✓	✓	✓	✓	The age at which SMA symptoms first appear significantly influences disease progression. The study reports that infants with neonatal onset (within the first month of life) generally have lower CHOP-INTEND scores and a more rapid decline in motor function. This early onset is associated with a mean decline rate of 1.71 points per month. Conversely, patients with onset after the neonatal period exhibit more variability in their progression, with age at baseline being a significant predictor of the rate of decline. These

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
									findings highlight the critical role of age at onset in the prognostic assessment of SMA patients.
4	Lin 2015	SMA Type	SMA Type	✓	✓	✓	✓	✓	Patients with type III SMA have less severe symptoms and are able to walk and reach the major motor milestones, but often lose the ability to walk over time as the disease progresses.
		Age onset	Age at symptom onset	✓	✓	✓	✓	✓	The weighted mean (standard deviation) ages of onset were 2.5 (0.6), 8.3 (1.6), and 39.0 (32.6) months for SMA types I, II, and III, respectively.
		Early diagnosis	Time between symptom onset and 1st DMT	✓	✓	✓	✓	✓	For studies reporting both age of onset and diagnosis, the weighted diagnostic delay was 3.6, 14.3, and 43.6 months for types I, II, and III, respectively.
		Region	Regional and cultural standards	✓	✓	✓	✓	✓	A subgroup analysis by region (data not shown) indicated that patients in North America appeared to have been diagnosed earlier than those in Europe or the Asia Pacific region.
5	Stevens 2020	SMA Type	SMA Type	✓	✓	✓	✓	✓	The paper discusses that the SMA type, determined largely by the number of SMN2 copies and the age at onset, is a crucial prognostic factor in determining the course of the disease and the potential response to treatments such as onasemnogene abeparvovecxioi. Early treatment, especially in SMA type 1, is associated with significantly better outcomes compared to later treatment, emphasizing the need for rapid diagnosis and management in these patients.
		SMN2 copy number	SMN2 copy number	✓	✓	✓	✓	✓	The paper highlights that individuals with more copies of the SMN2 gene typically exhibit less severe disease symptoms. This correlation is crucial as it affects the expected treatment outcomes with

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
									onasemnogene. Those with fewer SMN2 copies tend to have a more severe form of SMA and may require more aggressive management strategies.
		Age Treatment initiation	Age at Treatment	✓	✓	✓	✓	✓	Early treatment, particularly before symptom onset, is emphasized in the paper as being critical for optimal outcomes. Infants treated at younger ages demonstrate significantly better motor function improvements and survival rates compared to those who receive treatment later in the disease course. The paper states that this early intervention is key to maximizing the therapeutic benefits of onasemnogene.
		Motoric function	CHOP-INTEND score	✓	✓	✓	✓	✓	The initial motor function, measured using the CHOP-INTEND scale, as a predictive factor for treatment response. The paper discusses that patients with higher baseline CHOP-INTEND scores before starting treatment tend to experience greater improvements post-treatment. This suggests that baseline motor capabilities are indicative of potential gains from therapy.
		Genetic factors	Genetic Modifiers	✓	✓	✓	✓	✓	Specific genetic modifiers, such as mutations in exon 7 of the SMN2 gene, are mentioned as influencing the clinical phenotype and thus the treatment response. The paper notes that these genetic factors can lead to variations in disease severity, which in turn affects how patients respond to gene therapy.
6	Wadman 2019	Age onset	Age at symptom onset	✓	✓	✓	✓	✓	Early onset before six months is indicative of a more severe form of SMA.
		SMN2 copy number	SMN2 copy number	✓	✓	✓	✓	✓	The number of copies of the SMN2 gene is crucial. Fewer copies (typically two) are associated with more severe disease.

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
		Genetic factors	Genetic factors	✓	✓	✓	✓	✓	Genetic mutations and deletions in the SMN1 gene are primary indicators of SMA.
		Respiratory Function	Respiratory Function	✓	✓	✓	✓	✓	Respiratory insufficiency is a significant factor affecting survival. The severity of respiratory muscle involvement directly impacts prognosis.
		Age Treatment initiation	Early Treatment Initiation	✓	✓	✓	✓	✓	The study emphasizes that all participants were less than seven months old at the time of inclusion, highlighting early age at treatment initiation as a key factor for better outcomes. Early intervention is noted as crucial due to the progressive nature of SMA type I, where earlier treatment can potentially preserve more motor neuron function.
		Motoric function	- HINE-2 score - CHOP-INTEND Scores	✓	✓	✓	✓	✓	A higher proportion of nusinersen-treated infants showed improvements in motor milestone response on the HINE-2 and the CHOP-INTEND compared to those receiving a sham treatment.
			Motor Milestone	✓	✓	✓	✓	✓	Head Control: 16 out of 73 nusinersen-treated infants achieved head control, compared to none in the control group. Ability to Sit Independently: 6 out of 73 in the treatment group achieved this milestone. Ability to Roll and Stand: Additional milestones like rolling and standing were achieved by some infants in the nusinersen group but not in the sham group, underlining the impact of nusinersen on motor function development.

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
7	Wadman 2020	Genetic factors	Genetic factors	✓	✓	✓	✓	✓	The presence of a homozygous deletion of the SMN1 gene is crucial for diagnosing SMA and has prognostic implications.
		Age onset	Age at symptom onset	✓	✓	✓	✓	✓	The age at which symptoms appear significantly impacts prognosis. SMA type II typically presents between six and 18 months, whereas SMA type III presents after 18 months.
		Motoric Function	- HFMSE score			✓	✓	✓	Baseline motor function score (HFMSE) is important for assessing disease severity and progression.
		SMN2 copy number	SMN2 copy number	✓	✓	✓	✓	✓	The number of copies of the SMN2 gene is a well-known prognostic factor. Generally, a higher number of SMN2 copies is associated with a milder disease phenotype.
		Respiratory Function	FVC measure			✓	✓	✓	Measures such as FVC are important for evaluating respiratory muscle strength and function, which can be severely affected in SMA.
8	Albrechtsen 2020 (included from google scholar)	SMN2 copy number	SMN2 copy number	✓	✓	✓	✓	✓	The paper mentions that the number of SMN2 copies did not influence outcomes" in the treatment with nusinersen. It also states that children with a higher copy number generally have a milder phenotype.
		Age Treatment Initiation	Age at treatment	✓	✓	✓	✓	✓	The paper states, "Improvements were strongest in younger children, and there was no difference between children with two or three SMN2 copies".
		Age onset	Age at symptom onset	✓	✓	✓	✓	✓	The review highlights that "children treated before neurological symptoms presented (presymptomatic SMA) had a near-normal motor development". Additionally, "Nusinersen treatment before the first neurological symptoms has been shown to improve

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
									survival and motor development in children with genetically diagnosed SMA".
		Early diagnosis	Neonatal screening	✓	✓	✓	✓	✓	The paper discusses the importance of newborn screening, stating "Genetic screening for spinal muscular atrophy and pre-symptomatic nusinersen start may lead to near-normal motor development". It further elaborates, "Newborn SMA screening may be implemented to facilitate presymptomatic treatment".
		SMA Type	SMA Type	✓	✓	✓	✓	✓	The differences in treatment outcomes based on SMA type are detailed: "For SMA type 1, nusinersen improved both survival without permanent respiratory support and development of motor function. For SMA types 2 and 3, nusinersen improved or stabilised motor function development".
		Respiratory funcion	Ventilatory Support	✓	✓	✓	✓	✓	The paper reports, "Nusinersen increased survival without permanent ventilatory support in children with SMA type 1". It also states, "Survival without permanent respiratory support" was defined as no death or need for permanent respiratory support (non-invasive ventilation or tracheostomy more than 16 hours/day for more than 21 days)".
9	Meylemans 2019	SMN2 genotype	Genotype of SMN2	✓	✓	✓	✓	✓	The paper mentions that the SMA phenotype is related to the copy number of the SMN2 gene. This is discussed in the context of the genetic basis of SMA, where the loss of function of both alleles of the SMN1 gene leads to decreased expression of SMN protein, causing motor neuron degeneration.
		Motoric function	HFMSE score	✓	✓	✓	✓	✓	Significant and meaningful changes from baseline in the HFMSE scores were observed in children with later-onset SMA treated

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
									with intrathecal nusinersen. More than half of the patients in the treatment group had a clinically meaningful increase in HFMSE score of at least three points, with the greatest improvements in younger children and those who received treatment early.
			Motor milestone	✓	✓	✓	✓	✓	There is a significant increase in the amount of infants with early-onset SMA treated with nusinersen who have a motor-milestone response according to the HINE-2. Additionally, a significant increase in CHOP-INTEND scores was noted.
10	Polido 2019	SMN2 genotype	Genotype of SMN2	✓	✓	✓	✓	✓	The paper notes that cognitive outcomes tend to be poorer in studies involving children with SMA type I, suggesting a direct correlation between the severity of motor impairment and cognitive impairment.
		Gastrostomy	Gastrostomy tube feeding			✓	✓	✓	Children with SMA type I may need mechanical ventilation, nursing care, gastrostomy, tracheostomy, and therapies (motor and respiratory physiotherapy, occupational therapy, speech therapy for alternative communication and dysphagia).
		Age onset	Age at symptom stage	✓	✓	✓	✓	✓	The review indicates that the developmental stage of the children plays a significant role, with earlier onset SMA types (like type I) showing more significant cognitive deficits.
		SMA Type	SMA Type	✓	✓	✓	✓	✓	The study highlights that the type of SMA significantly influences cognitive outcomes. Children with SMA type I, who often have the most severe form of the disease, tend to show poorer cognitive performance, particularly in visual and auditory attention and executive function tasks. In contrast, children with types II and III SMA generally demonstrate better cognitive outcomes.

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
11	Wijngaarde 2017	SMN2 copy number	SMN2 copy number	✓	✓	✓	✓	✓	This genetic factor was discussed as influential in determining the severity of SMA, with lower SMN2 copy numbers leading to more severe forms of SMA and associated cardiac abnormalities. The paper details this correlation, noting that an over-representation of patients with SMA type 1 who also had cardiac defects had only one SMN2 copy.
		SMA Type	SMA Type	✓	✓	✓	✓	✓	The paper mentions that cardiac rhythm disorders, including various arrhythmias and conduction abnormalities, were more frequently reported in patients with milder forms of SMA (e.g., SMA type 3), compared to those with more severe forms (SMA type 1).
12	Bedi 2018	SMA Type	SMA Type	✓	✓	✓	✓	✓	Studies focusing on SMA1 reported decreased hospitalizations and prolonged survival as outcomes of NIV use. The review notes that about 50% of studies reported decreased hospitalizations, and 75% reported on mortality outcomes, highlighting NIV's role in improving the management of respiratory insufficiencies in SMA1.
		Multiple Disorders	Multiple Disorders			✓	✓	✓	For infants with multiple disorders, the review synthesized results across studies, noting that outcomes varied significantly based on individual conditions and their severities. This category included infants with more than one underlying condition affecting their respiratory status.
13	Moore 2016	Gastrostomy	Gastrostomy tube feeding	✓		✓	✓		There is variability in nutritional management practices internationally, with different approaches noted in the use of gastrostomy tubes and dietary interventions. These variations emphasize the need for personalized nutritional management to optimize care.

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
		Nutrition	Over/Under-nutrition	✓	✓	✓	✓	✓	The review indicates that body composition is often abnormal in patients with SMA, showing increased fat mass and decreased fat-free mass. This is crucial as it impacts nutritional status and management approaches.
			Feeding and Swallowing Issues	✓	✓	✓	✓	✓	Feeding and swallowing difficulties are prevalent in SMA types I and II, complicating nutritional intake and increasing the risk of severe complications such as aspiration pneumonia. The review discusses the association of these issues with the severity of disease and functional abilities, such as sitting and head control.
14	Landfeldt 2019	SMA type	SMA type	✓	✓	✓	✓	✓	According to the findings, the type of SMA significantly impacts quality-of-life. For example, more severe types (like SMA Type I) generally correlate with lower quality-of-life scores compared to milder forms (SMA types II and III).
15	Alhammoud 2021	SMA Type	SMA Type	✓	✓	✓	✓	✓	The distribution of SMA types and their associated prognostic implications are detailed in the "Results" section, particularly noting the prevalence of type II SMA and its early and rapid deterioration compared to type III.
		Age Treatment initiation	Age at treatment	✓	✓	✓	✓	✓	The average age at surgical intervention and its implications on the natural history and postoperative outcomes are discussed in the "Results" and "Discussion" sections of the paper.
		Complications	Complications	✓	✓	✓	✓	✓	The "Results" section and the table summarizing post-operative complications detail the common spine-related and chest-related complications and their potential impact on patient outcomes post-surgery.

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				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
16	Baranello 2021	SMN2 Copy Number	SMN2 Copy Number	✓	✓	✓	✓	✓	The influence of the SMN2 copy number on survival and disease severity is extensively reviewed. It is mentioned that in untreated infants with type 1 SMA, a higher SMN2 copy number is associated with increased survival.
		Age onset	Age at Symptom Onset			✓			The paper reports that in type 1 SMA, infants with later symptom onset exhibit prolonged survival compared to those with symptoms at birth.
		Age Treatment Initiation		✓	✓	✓	✓	✓	The age at treatment initiation is highlighted as a treatment-effect modifier, particularly noting its impact on the outcomes of disease-modifying therapies across different SMA types.
		Genetic factors	Presence of NAIP Gene	✓	✓	✓			The presence of the NAIP gene is associated with increased survival in infants with type 1 SMA. Higher NAIP copy numbers contribute to a longer median survival, reinforcing its role as a prognostic factor.
17	Bischof 2021	Motor function	CHOP INTEND score	✓	✓	✓	✓	✓	The CHOP INTEND score is highlighted as a validated motor outcome measure developed specifically for infants with SMA type 1, used to quantify the natural decline of motor function for infants not receiving disease-modifying therapy.
		Nutrition	Nutritional Support	✓	✓	✓	✓	✓	Nutritional support is noted as a critical indicator of disease progression, especially as bulbar dysfunction is universal among patients with severe SMA, leading to increased feeding and swallowing difficulties, weight loss, pulmonary aspiration, and the need for mechanical feeding.

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
		Age onset	Age at Symptom Onset			✓	✓	✓	The age at which symptoms first appear is indicated in the baseline characteristics of the study population, which helps to categorize the severity and prognosis of SMA at an early stage.
		Age treatment initiation	Age at treatment	✓	✓	✓	✓	✓	The baseline characteristics include the age at study start, which is significant for understanding when treatment was initiated and its potential impact on treatment outcomes.
		SMN2 Copy Number	SMN2 Copy Number	✓	✓	✓	✓	✓	This is identified as a key prognostic factor that influences the severity of the disease; more copies of the SMN2 gene generally correlate with a milder phenotype of SMA. The paper details the role of SMN2 copy number in predicting disease severity and treatment outcomes.
18	Cobo-Vicente 2021	Age onset	Age at Symptom Onset	✓	✓	✓	✓	✓	The paper discusses the impact of the age and timing of disease onset on prognosis in the "Study Characteristics" section, highlighting that earlier onset often correlates with more severe disease forms and worse outcomes.
		SMN2 Copy Number	SMN2 Copy Number	✓	✓	✓	✓	✓	The "Study Selection" section describes the influence of genetic factors, particularly SMN2 gene copy number variations, on disease severity and prognosis.
		Nutrition	Bone mineral density			✓	✓	✓	The review highlights that NMES contributes to positive changes in body composition, specifically noting improvements in bone mineral density.
19	Coratti 2021	SMA Type	SMA Type				✓	✓	The overall effect of nusinersen across different ages and SMA types is discussed in the conclusion section of the paper, highlighting that the benefits are observed irrespective of age.

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
		Motoric function	HFMSE				✓	✓	The study details improvements in HFMSE scores in treated patients on pages 3 and 4, highlighting subgroup analyses by age and SMA type.
			RULM score				✓	✓	Improvements in RULM scores and significant subgroup differences are discussed where the paper emphasizes better outcomes in pediatric patients and SMA type 2.
			6MWT				✓	✓	The results and significance of improvements in the 6MWT are mentioned on pages 6 and 7, with reference to both adult and pediatric populations.
20	Kennedy 2020	Age onset	Age at Symptom Onset	✓	✓	✓	✓	✓	The paper indicates that increasing age are associated with slower walking speeds in children with neuromuscular diseases, including SMA. This is specifically discussed in the context of SMA type 3, congenital muscular dystrophy, and Duchenne muscular dystrophy as these conditions are linked to more limited endurance and ambulatory capacity.
		Motoric function	Highest motor milestone at baseline	✓	✓	✓	✓	✓	Muscle weakness, as the primary impairment in neuromuscular diseases affecting children, is noted to have a profound impact on gait and functional ambulation. This factor leads to problems such as poor standing balance, increased falls, and reduced mobility, especially highlighted in conditions like SMA.
			6MWT	✓	✓	✓	✓	✓	The paper reviews assessments of gait and functional ambulation, mentioning the use of endurance and functional tests like the 6MWT and the 10m walk/run test. It notes that the six-minute walk distance is significantly reduced in paediatric neuromuscular diseases, including SMA.

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
21	Abbas 2022	Age onset	Age at symptom onset	✓	✓	✓	✓	✓	The paper details the classification of SMA into different types based on age of onset and further explains how these classifications affect the study population and outcomes observed in the trials.
		SMN2 copy numbers	SMN2 copy numbers	✓	✓	✓	✓	✓	The genetic background, specifically mutations or deletions in the SMN1 gene and the compensatory role of SMN2 gene copies, is discussed and explains the biological underpinnings of SMA and its impact on motor neuron survival and function.
		Motor function	HINE-2 scores	✓	✓	✓	✓	✓	Efficacy of nusinersen, including significant improvements in motor milestones and HINE-2 scores, is detailed. The results indicate a significant risk difference in motor milestone response and improvement in the HINE-2 score in the nusinersen group compared to the control group.
22	AlBalawi 2022	Respiratory function	Ventilation support	✓	✓	✓	✓	✓	The paper indicates that children with SMA type 1 using long-term NIV generally have higher mortality rates compared to those using IMV. However, for SMA types other than type 1, NIV may be as effective as IMV in reducing mortality.
23	Angeli 2022	SMA Type	SMA Type	✓	✓	✓	✓	✓	The type of SMA, which critically influence progression and respiratory outcomes, are detailed in the Introduction section, which outlines the characteristics of SMA types I through IV and their respective impact on muscle function and survival.
		Respiratory Function	Airway secretion clearance	✓	✓	✓	✓	✓	The progressive decline of respiratory function due to muscular weakness is discussed in the Discussion section. This deterioration is attributed to inspiratory and expiratory muscle weakness, poor

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
									airway secretion clearance, feeding and swallowing difficulties, and reduced chest wall compliance.
		Genotype of SMN2	Genotype of SMN2	✓	✓	✓	✓	✓	The genetic basis of SMA, specifically mutations in the SMN1 gene, is a fundamental prognostic factor. The number of copies of the SMN2 gene can modify the severity of the disease, influencing motor function outcomes and survival.
		Age onset	Age at symptom onset	✓	✓	✓	✓	✓	The paper describes how the age at symptom onset is a critical prognostic factor, with earlier onset (as seen in type I SMA) associated with more severe disease and poorer outcomes.
24	Erdos 2022	SMA Type	SMA Type	✓	✓	✓	✓	✓	The impact of SMA type on treatment outcomes is discussed throughout the paper. For example, it mentions that "nusinersen improved motor functions in SMA type 1 patients, while in SMA type 2 to type 4 patients stabilisation or small improvements" were observed.
		Age Treatment initiation	Early treatment initiation	✓	✓	✓	✓	✓	The paper states that "infants who initiate treatment prior to the onset of clinical signs of SMA, show considerable contrast to the natural history of untreated SMA".
		Nutrition	Nutritional Support	✓	✓	✓	✓	✓	The need for respiratory and nutritional support as quality-of-life indicators is highlighted in several parts of the paper, indicating these needs as measures of disease progression and treatment response.
		SMN2 Copies numbers	SMN2 Copies numbers	✓	✓	✓			The influence of the number of SMN2 copies on disease severity and response to treatment is mentioned in the introduction and background of the paper.

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
25	Gavriilaki 2022 (Biomarker)	Motor function	- HFMSE test - 6MWT		✓	✓	✓	✓	The paper discussed the adaptation of scales such as the HFMSE and the 6MWT. These tests measure SMA progression but it remains uncertain whether small improvements are clinically significant.
			Highest motor milestone at baseline		✓	✓	✓	✓	Muscle strength was frequently assessed using the MRC score and HHD. The progression of muscle strength, particularly measured by novel devices like MyoGrip and MyoPinch dynamometers, showed significant declines in some cohorts.
		Respiratory function	Lung function		✓		✓	✓	Lung function tests are described as stable across different studies, which might indicate their insensitivity to depicting progression in SMA. The stability of lung function is particularly noted across different cohorts, suggesting its limited utility as a biomarker for SMA progression.
		Biomarkers	Neurophysiologic Biomarkers		✓	✓	✓	✓	Neurophysiologic measures such as CMAP and MUNE are emphasized for their potential in illustrating the natural history of SMA by quantifying motor neuron loss and compensatory reinnervation.
			Other biomarkers				✓	✓	MRI assessments of the central and peripheral nervous system were undertaken in several studies. The data suggests potential utility, but more robust and longitudinal research is required to validate MRI as a reliable biomarker for monitoring SMA progression.
26	Gavriilaki 2022 (2)	SMA Type	SMA Type	✓	✓	✓	✓	✓	The effectiveness of nusinersen was more notable in SMA types 3 and 4, particularly in the short-term. This is discussed in the paper

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
	(Nusinersen)								where improvements in HFMSE and RULM scores are mentioned, showing better responses in these SMA types.
		SMN2 Copy Number	SMN2 Copy Number	✓	✓	✓	✓	✓	While the specific discussion on SMN2 copy number and its impact on prognosis is not explicitly detailed in this paper, it is widely recognized in literature and briefly mentioned in the paper where the genetic basis of SMA, including the role of SMN1 and SMN2, is explained.
		Age onset	Age at symptom onset	✓	✓	✓	✓	✓	The paper mentions that nusinersen is effective even in patients with a longer disease duration. This indicates that age and the duration of the disease at the onset of treatment can influence outcomes.
		Motoric function	- HFMSE test - RULM test	✓	✓	✓	✓	✓	Motor function as a prognostic factor is evident from the motor function scales (HFMSE, RULM) used to measure the efficacy of nusinersen, with initial functional status impacting the degree of observed improvement.
27	Ribero 2022	SMA Type	SMA Type	✓	✓	✓	✓	✓	Type of SMA are discussed in the paper, outlining the differences in disease progression among Types 0-4, with Type 0 being the most severe, typically presenting prenatally and requiring immediate respiratory support.
		Age onset	Age at symptom onset	✓	✓	✓	✓	✓	The paper mentions that infants with type 1 SMA present with symptoms before 6 months of age, which typically correlate with more severe disease and worse prognosis if untreated.
		Motoric function	CHOP-INTEND score	✓	✓	✓	✓	✓	Baseline motor function is a critical prognostic factor. The paper notes the use of the CHOP-INTEND scale to assess motor function

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
									in infants with type 1 SMA, indicating that lower scores correlate with more severe disease.
		SMN2 Copy Number	SMN2 Copy Number	✓	✓	✓	✓	✓	The SMN2 copy number is referenced as a prognostic factor affecting disease severity. Patients with more SMN2 copies generally have a less severe form of SMA and a better prognosis.
28	Wu 2022	SMN2 Copy Number	SMN2 Copy Number	✓	✓	✓	✓	✓	The paper highlights the role of SMN2 copy number as a major determinant of disease severity, impacting the range of clinical features. The paper discusses the function of the SMN2 gene and its variable copy number across patients.
		Age onset	Age at symptom onset	✓	✓	✓	✓	✓	The classification of SMA types based on the age of onset and motor milestones is detailed in Table 1. This table outlines how early or later onset affects the clinical presentation and progression of the disease.
		Motoric function	Motoric function	✓	✓	✓	✓	✓	Table 1 also details the maximal motor function achieved by patients with different SMA types, indicating the prognosis associated with each type based on motor development.
29	Yang 2022	SMN2 Copy Number	SMN2 Copy Number	✓	✓	✓	✓	✓	The genetic mutation in the SMN1 gene and the number of SMN2 gene copies are critical. The paper discusses the role of these genetic components in determining the severity of SMA, noting that a smaller number of SMN2 copies is associated with a more severe disease phenotype.
		Age onset	Age at symptom onset	✓	✓	✓	✓	✓	The paper mentions that the age at which symptoms first appear is a significant determinant of disease severity. Early onset, particularly before 6 months (type 1 SMA), is linked to more severe disease

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
		Motoric function	Motoric function	✓	✓	✓	✓	✓	Baseline motor function and its progression are highlighted as important prognostic indicators. The paper states that higher initial motor function and slower progression of motor function loss are associated with better long-term outcomes
		Respiratory function	Respiratory complication	✓	✓	✓	✓	✓	The paper emphasizes the importance of respiratory function, noting that respiratory complications are a major cause of morbidity and mortality. It mentions the impact of ventilatory support on patient outcomes, particularly the need for permanent ventilation.
		Nutrition	Nutritional support	✓	✓	✓	✓	✓	The need for nutritional support and its impact on disease progression and quality-of-life are discussed. The paper points out that adequate nutritional management is crucial for maintaining patient health and potentially improving outcomes.
30	Al-Taie 2023	Genetic Factors	SMN1 Gene Mutations	✓	✓	✓	✓	✓	The paper emphasizes that SMA results from mutations or deletions in the SMN1 gene, which is crucial for motor neuron survival. This genetic basis directly impacts disease severity and is mentioned as the primary cause of the condition.
		SMN2 Copy Number	SMN2 Copy Number	✓	✓	✓	✓	✓	The number of copies of the SMN2 gene significantly influences disease severity and patient outcomes, as SMN2 partly compensates for the loss of SMN1. More copies are generally associated with milder forms and later onset of SMA.
		Age onset	Age at symptom onset	✓	✓	✓	✓	✓	As described in the paper, SMA type 1, the most severe form, typically presents within the first six months of life, affecting prognosis significantly compared to other types, which manifest later.
		Motoric function	HINE-2 score CHOP-INTEND score	✓	✓	✓	✓	✓	The paper outlines how baseline motor functions, assessed through various scales like HINE-2 and CHOP-INTEND, serve as

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
									prognostic indicators. Better initial function typically suggests a milder disease progression.
		Respiratory Function	Ventilatory support	✓	✓	✓	✓	✓	The paper discusses the vital role of respiratory function as a prognostic factor. SMA, particularly types 1 and 2, often involves significant respiratory muscle weakness, necessitating support like ventilatory assistance, which correlates with disease severity and survival rates.
		Nutrition	Nutritional support	✓	✓	✓	✓	✓	The paper highlights the importance of managing nutritional needs due to difficulties in swallowing and feeding, which are more pronounced in severe cases. Effective nutritional management can impact overall health outcomes and quality-of-life.
31	Aragon-Gawinska 2023	SMN2 Copy Number	SMN2 Copy Number	✓	✓	✓	✓	✓	The number of SMN2 copies is a primary prognostic factor for SMA severity. The paper states, "the level of SMN protein produced from SMN2 copies is inversely correlated with disease severity" and "the SMN2 copy number is the main, but not the only prognostic factor of SMA type. Specific findings include: - About 86% of patients with SMA type 1 have two copies of SMN2. - 87% of patients with SMA type 2 have three copies of SMN2. - 64% of patients with SMA type 3 have three copies of SMN2 and 31% have four copies of SMN2.
		Age Treatment Initiation	Age at Treatment Initiation	✓	✓	✓	✓	✓	Early initiation of treatment is emphasized as critical. The paper states, "clinical trial results indicated that disease-modifying

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
									treatments are highly effective when given prior to symptom onset. Specific data shows, "Among 35 patients with three SMN2 copies treated before 42 days of age and followed-up for at least 18 months, all but one achieved autonomous ambulation".
		Motoric function	Highest motor milestone at baseline	✓	✓	✓	✓	✓	Achieving motor milestones is a key indicator of prognosis. The paper discusses, "Of 41 patients with two SMN2 copies, who were non-symptomatic at treatment initiation, all achieved a sitting position independently and 31 were able to walk.
		Respiratory funcion	Ventilation support	✓	✓	✓	✓	✓	12% used non-invasive ventilation at last follow-up.
		Nutrition	Nutritional support	✓	✓	✓	✓	✓	The need for nutritional support is highlighted as a prognostic factor. The paper mentions, "Among patients with two copies of SMN2, 8% had nutritional support".
		Genetic factors	Genetic Modifiers	✓	✓	✓	✓	✓	Variants in SMN2 and other genetic modifiers influence disease severity. The paper refers to mutations in SMN2 also modify the severity of SMA" and highlights the c.859G > C variant, which "promotes exon 7 inclusion, increasing the amount of correct SMN protein produced".
32	Gavriilaki 2023	SMA type	SMA type	✓	✓	✓	✓	✓	The study reported that CSF GFAP levels decreased significantly in treated SMA type 3 but not in type 2 patients, showing that the type of SMA influences biomarker responses.

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
		Age onset	Age at symptom onset	✓	✓	✓	✓	✓	The paper included patients aged 11 to 72 years, highlighting that age and disease duration can influence treatment outcomes and the progression of SMA.
		SMN2 copy numbers	SMN2 copy numbers	✓	✓	✓	✓	✓	The paper mentioned that CSF protein and Qalb levels were correlated with the number of SMN2 gene copies, indicating the impact of genetic factors on disease severity and treatment response.
33	Jiang 2023	Age onset	Age at symptom onset	✓	✓	✓	✓	✓	The age at which the first treatment dose is administered is considered a significant predictor of treatment response.
		Age Treatment Initiation	Age at treatment	✓	✓	✓	✓	✓	This is highlighted as one of the strongest predictors of treatment response and is crucial for accurate assessment of SMA treatment outcomes.
		Nutrition	Nutritional Support	✓		✓			Factors such as the use of feeding tubes and the extent of baseline differences in swallowing and feeding difficulties across trial populations are also significant.
		Motoric Function	HFMSE score RULM score			✓	✓	✓	Scores from assessments like the HFMSE or the RULM are used to measure motor function at the start of treatment and are critical for evaluating treatment efficacy.
		SMN2 Copy Number	SMN2 Copy Number	✓	✓	✓	✓	✓	The number of SMN2 gene copies is a genetic factor that significantly influences disease severity and treatment response.
		Respiratory Function	Ventilatory Support	✓		✓			The need for ventilatory support at baseline is an important prognostic factor. This includes variations in definitions across different trials, impacting the comparability of results.
34	Qiao 2023	Age onset	Age at symptom onset	✓	✓	✓	✓	✓	SMA type I is the most common phenotype, occurring in the first six months of life, and it is associated with functional impairments and progressive weakness of the respiratory muscles, leading to a

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
									high rate of infant mortality or invasive ventilation by 2 years of age.
		SMN2 copy numbers	SMN2 copy number	✓	✓	✓	✓	✓	The SMN2 copy number is negatively correlated with disease severity and a higher level of functional SMN protein is associated with milder phenotypes.
		Motor Function	- HFMSE score - RULM score - HINE-2 score	✓	✓	✓	✓	✓	It is reported that nusinersen treatment was beneficial for increasing the score of the HFMSE (WMD: 4.90; 95% CI: 3.17, 6.63; $p < 0.00001$), RULM (WMD: 3.70; 95% CI: 3.30, 4.10; $p < 0.00001$), and HINE-2 (WMD: 5.21; 95% CI: 4.83, 5.60; $p < 0.00001$). In addition, the risdiplam treatment group also showed statistically significant improvements in the HFMSE score (WMD:0.87; 95% CI: 0.05, 1.68; $p = 0.04$), and (WMD: 1.29; 95% CI: 0.57, 2.01; $p = 0.0005$).
35	Yang 2023	Age onset	Age at symptom onset	✓	✓	✓	✓	✓	Patients older than 8 months were more likely to experience adverse events such as thrombocytopenia (79.3%) and elevated aminotransferases (71.7%) compared to younger patients (5% and 28.5%, respectively).
		Age Treatment Initiation	Early treatment	✓	✓	✓	✓	✓	SMA patients diagnosed and treated at a younger age tend to have better outcomes. The age at dosing with onasemnogene abeparvovec ranged from 0.5 to 59 months, and younger patients generally showed better responses.
		SMN2 Copy Number	SMN2 Copy Number	✓	✓	✓	✓	✓	SMN2 is the highly homologous copy of SMN1 while only yielding 10% of full-length SMN protein. Hence, the copy number of SMN2 is negatively associated with disease severity.

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
									Pooled incidence rate of at least one new motor-milestone achievement was 84.5% in the 'two SMN2 copy numbers' group and 81.9% in the 'three SMN2 copy numbers' group.
		SMA type	SMA type	✓	✓	✓	✓	✓	The type of SMA (e.g., type 1, type 2) influences prognosis. Most patients in the study were of SMA type 1, which is associated with a more severe prognosis but also showed significant improvement with gene therapy.
		Motoric Function	Motoric function	✓	✓	✓	✓	✓	Higher baseline motor function, as assessed by tools such as the CHOP-INTEND score, is indicative of better treatment outcomes. Maintenance of CHOP INTEND scores ≥40 points was observed in 86.9% of patients during long-term follow-up, indicating significant improvement in motor function.
36	Zhong 2023	Age onset	Age at symptom onset	✓	✓	✓	✓	✓	Early onset SMA, particularly before 6 months of age, is associated with a more severe disease course and poorer prognosis. Later onset types, such as SMA types 2 and 3, generally have a better prognosis due to milder symptoms and slower disease progression.
		SMN2 copy numbers	SMN2 copy numbers	✓	✓	✓	✓	✓	The number of copies of the SMN2 gene significantly influences the severity of SMA. Individuals with more SMN2 copies usually exhibit milder symptoms and a better prognosis compared to those with fewer copies.
		Motoric function	Motoric function	✓	✓	✓	✓	✓	Baseline motor function at the time of diagnosis is crucial. Patients presenting with better motor function at diagnosis tend to have a more favourable prognosis and respond better to treatments like nusinersen.

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
		Nutrition	Nutritional support	✓	✓	✓	✓	✓	Proper nutritional management is vital. Malnutrition or poor nutritional status can worsen the prognosis, whereas good nutritional status supports overall health and enhances treatment efficacy.
		Respiratory function	Respiratory function	✓	✓	✓	✓	✓	Baseline respiratory function is a significant prognostic factor, as respiratory complications are a primary cause of morbidity and mortality in SMA. Better baseline respiratory function is associated with improved outcomes.
37	Bellai 2024	Age onset	Age at symptom onset	✓	✓	✓	✓	✓	Earlier onset of weakness is linked to higher numbers of CAG repeats. Eleven of the thirteen articles identified a statistically significant inverse correlation between CAG repeat length and age of weakness onset in SBMA.
		Motoric function	ADL Scores	✓	✓	✓	✓	✓	Functional disability progresses slowly in SMA patients. ADL scores, which measure the impact of muscle weakness on daily activities, correlate with both age and CAG repeat number.
38	Dosi 2024	SMN2 Copy Number	SMN2 Copy Number		✓	✓	✓	✓	SMN2 copy number is strongly correlated with SMA phenotype in patients with SMN1 deletion, while no correlation was found in patients with an SMN1 mutation. Patients with three SMN2 copies show a highly variable clinical phenotype ranging from severe (type I) to mild (type IIIc).
		Age onset	Age at symptom onset	✓	✓	✓	✓	✓	In type I SMA, patients with three SMN2 copies typically show a later onset of symptoms compared to those with two SMN2 copies. The mean age at onset in type I SMA with three SMN2 copies varies, with studies reporting onset at 1-3.5 months.

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
									For types II and III SMA, the mean age at clinical onset is lower in patients with three SMN2 copies compared to those with four copies.
		Motor Function	HFMSE scores		✓	✓	✓	✓	Patients with three SMN2 copies generally exhibit a slower decline in motor function compared to those with two copies. For instance, HFMSE scores tend to be better in patients with three SMN2 copies in cross-sectional studies.
		Biomarkers	Neurophysiologic Biomarkers	✓	✓	✓	✓	✓	Compound Muscle Action Potential amplitude is significantly related to SMN2 copy number and may serve as a sensitive measure of motor function impairment in infants before symptoms develop.
			Other biomarkers	✓	✓	✓	✓	✓	Other biomarkers, including NAIP copy number, PLS3, coronin 1C expression, SMN protein levels, microRNA, neurofilament proteins, creatine kinase, creatinine levels, and Tau levels in CSF, are being considered to further guide prognosis and treatment response.
39	Pascual-Morena 2024	Age Treatment initiation	Early treatment	✓	✓	✓	✓	✓	The paper highlights the significance of early treatment initiation. "The limited available evidence suggests that risdiplam is an effective and safe drug for the treatment of SMA. In addition, long-term clinical benefit may be partly determined by the stage of disease at which treatment is initiated".
		Motor Function	CHOP-INTEND Score	✓	✓	✓	✓	✓	After 12 months of treatment, 57% of participants with SMA1 achieved a CHOP-INTEND score ≥40 points, and more than half were able to feed orally and had head control.
			RULM HFMSE Scores	✓	✓	✓	✓	✓	In SMA2/3 RULM, and HFMSE increased by 2.09 (1.17, 3.01), 1.73 (1.25, 2.20), and 1.00 (0.40, 1.59) points, respectively.

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
			Highest motor milestone at baseline	✓	✓	✓	✓	✓	In SMA1 or probable SMA1 (i.e., two copies of SMN2), CHOP-INTEND ≥40 points was achieved in more than half of the participants at 12 months, and in 100% of the presymptomatic participants. At 24 months, 76% of participants achieved CHOP-INTEND ≥40 points. In addition, 85% were able to feed orally, 71% had head control, 44% were able to sit for >30 s, and 90% did not require permanent ventilatory support at 24 months.
		Respiratory Function	Respiratory Function	✓	✓	✓	✓	✓	In SMA2/3, FVC and FEV1 tended to decrease at 12 and 24 months, while PCF remained stable and SNIP tended to improve. Efficacy on respiratory function in SMA2/3 was inconsistent.
		SMN2 copy numbers	SMN2 copy number	✓	✓	✓	✓	✓	There are various phenotypes of SMA, which are largely correlated by the copies of the SMN2 gene. SMA type 1 [SMA1, MIM: 253300]. Patients with SMA1 usually have one or two copies of the SMN2 gene. SMA type 2 [SMA2, MIM: 253550]. Patients with SMA2 usually have three copies of the SMN2 gene. Finally, SMA type 3 [SMA3, MIM: 253400]. Patients with SMA3 usually have three or four copies of the SMN2 gene.

Abbreviations: 6MWT: 6-Minute Walk Test, ADL: Activities of Daily Living, CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, CI: Confidence Interval, CMAP: Compound Muscle Action Potential, CSF: Cerebrospinal Fluid, FEV1: Forced Expiratory Volume 1, GFAP: Glial Fibrillary Acidic Protein, GMFM: Gross Motor Function Measure, HFMSE: Hammersmith Functional Motor Scale Expanded, HHD: Handheld Dynanometry, HINE: Hammersmith Infant Neurological Exam, IMV: Intermittent Mandatory Ventilation, MRC: Medical Research Council, MUNE: Motor Unit Number Estimation, NAIP: Neuronal Apoptosis Inhibitory Protein, NIV: Non Invasive Ventilation, NMES: Neuromuscular Electrical Stimulation, PCF: Peak Cough Flow, RULM: Revised Upper Limb Module, SBMA: Spinal and Bulbar Muscle Atrophy, SMA: Spinal Muscular Atrophy, SNIP: Sniff Nasal Inspiratory Pressure, WMD: Weighted Mean Difference.

Table 14: Details of confounders /prognostic factors from included guidelines and recommendations

#	Study **ID**	**Prognostic factor**	**Characteristics**	**Relevance for**					**Details**
				Pre-symptomatic 1/2 SMN2 copies	**Pre-symptomatic 3 SMN2 copies**	**SMA Type I**	**SMA Type II**	**SMA Type III**	
1	NICE Guidelines 2016	Age onset	Age at symptom onset	✓	✓	✓	✓	✓	Younger age at onset generally correlates with a better prognosis.
		Early diagnosis	Time between diagnosis or symptom onset and start of treatment	✓	✓	✓	✓	✓	Longer delay between symptom onset and diagnosis is associated with a poorer prognosis.
		Respiratory Function	FVC measure	✓	✓	✓	✓	✓	Poor respiratory function at diagnosis, such as lower FVC, is a predictor of shorter survival.
		Gastrostomy	Gastrostomy	✓	✓	✓	✓	✓	Presence and timing of gastrostomy can influence prognosis.
		Genetic factors	Genetic factors	✓	✓	✓	✓	✓	Certain gene mutations associated with familial forms of MND may also play a role in prognosis.
2	Oliver 2017	Respiratory Function	FVC measure	✓	✓	✓	✓	✓	Poor respiratory function at diagnosis is linked to a worse prognosis.
		Early diagnosis	Time between diagnosis or symptom onset and start of treatment	✓	✓	✓	✓	✓	A shorter time from the onset of symptoms to the time of diagnosis is associated with a poorer prognosis.
3		SMN2 copy number	SMN2 copy number	✓	✓	✓	✓	✓	In paediatric patients, the maximum motor developmental milestone achieved (SMA types 0-3) and the number of

#	Study **ID**	**Prognostic factor**	**Characteristics**	**Relevance for**					**Details**
				Pre-symptomatic 1/2 SMN2 copies	**Pre-symptomatic 3 SMN2 copies**	**SMA Type I**	**SMA Type II**	**SMA Type III**	
	Castellano 2022								SMN2 copies, the main prognostic factors used before the new treatments were developed, continue to be relevant.
		Motoric function	Highest motor milestone at baseline	✓	✓	✓	✓	✓	SMA has traditionally been classified into 5 broad categories according to the maximum motor developmental milestone achieved and the age of clinical onset; this enables us to establish a working prognosis in untreated patients.
		Complications	Complications	✓	✓	✓	✓	✓	Presence of scoliosis, history of scoliosis surgery, or contractures.
4	Milligan 2022	SMN2 copy number	SMN2 copy number	✓	✓	✓	✓	✓	The number of SMN2 gene copies is a significant prognostic factor, as the severity of SMA inversely correlates with SMN2 copy number. More copies generally lead to a less severe phenotype.
		Genetic factors	SMN1 Gene Mutations	✓	✓	✓	✓	✓	The presence of hybrid genes, which combine elements of SMN1 and SMN2, can result in increased exon 7 inclusion in SMN mRNAs, leading to higher levels of functional SMN protein and a milder SMA phenotype.
		Early diagnosis	Time between symptom onset and 1st DMT	✓	✓	✓	✓	✓	Early diagnosis through newborn screening and subsequent determination of SMN2 copy number and disease-modifying variants are critical for prognosis. Early treatment can halt neuron degeneration and significantly improve outcomes.
5	Abiusi 2023	SMN2 copy number	SMN2 copy number	✓	✓	✓	✓	✓	The number of SMN2 gene copies is inversely related to disease severity. Patients typically have two to four copies of the SMN2 gene, and a higher copy number generally indicates a milder phenotype.
		Early diagnosis	Neonatal screening	✓	✓	✓	✓	✓	The implementation of genetic testing and NBS for SMA allows for early diagnosis and treatment, which can significantly improve outcomes. The study emphasizes the

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
									importance of standardized SMN2 copy number assessment and testing for SMN2 splicing-modifier variants in NBS programs.
6	Michelson 2018	SMN2 genotype	Genotype of SMN2	✓	✓	✓	✓	✓	The prognostic importance of SMN1 and SMN2 gene mutations or deletions is highlighted, with evidence showing that infants with homozygous deletions or mutations in SMN1 improve their probability of permanent ventilation-free survival when treated with nusinersen compared to historical controls.
		Age Treatment initiation	Age at treatment	✓	✓	✓	✓	✓	The paper provides Class I evidence supporting that infants with SMA and 2 copies of the SMN2 gene benefit significantly from early treatment initiation (younger than 7 months), which results in better motor milestone responses and higher rates of event-free survival than the sham control.
7	Amin 2017	Gastrostomy	Gastrostomy placement	✓	✓	✓	✓	✓	The use of gastrostomy tube feeds is highlighted as one of the three significant factors that improve survival for children with SMA. This intervention helps manage nutrition effectively, particularly in patients who have difficulties with oral intake.
		SMA type	SMA type	✓	✓	✓	✓	✓	The severity and prognosis of SMA vary by type. Type 1 (Werdnig-Hoffman disease) is the most severe, with onset between birth and 6 months and a life expectancy of less than 2 years. Type 2 has onset before 18 months, with patients able to sit but not stand, and death generally occurs after age 2. Type 3 is the mildest form, with onset after 18 months and a normal life expectancy.

#	Study **ID**	**Prognostic factor**	**Characteristics**	**Relevance for**					**Details**
				Pre-symptomatic 1/2 SMN2 copies	**Pre-symptomatic 3 SMN2 copies**	**SMA Type I**	**SMA Type II**	**SMA Type III**	
		Age onset	Age at symptom onset	✓	✓	✓	✓	✓	The age at which symptoms first appear significantly influences the disease trajectory and overall prognosis.
		Respiratory function	Ventilatory Support	✓	✓	✓	✓	✓	The use of NIV and invasive ventilation significantly impacts survival rates and quality-of-life. NIV improves the respiratory disturbance index, sleep architecture, and overall survival. The use of MI-E devices and gastrostomy tube feeds are crucial factors that improve survival.
		Nutrition	Nutritional support	✓	✓	✓	✓	✓	Aggressive nutritional management has contributed to improved survival rates. Proper nutrition is vital for maintaining muscle strength and overall health, which can affect the progression of SMA.
8	Solé 2020	Response to Treatments	Response to Treatments	✓	✓	✓	✓	✓	The patient's response to ongoing treatments, especially those involving immunosuppressive and immunomodulating therapies, impacts their prognosis. Continued treatment without manifestations suggestive of COVID-19 is recommended to avoid disease relapse.
		Age Treatment initiation	Age Treatment initiation	✓	✓	✓	✓	✓	For children with type 1 or type 2 SMA, the initiation of treatment with nusinersen is considered a therapeutic emergency because delaying treatment can have severe functional and vital consequences. For adolescents and adults with type 2 and type 3 SMA, the therapeutic objective is more focused on stabilizing or slightly improving the functional state, allowing for some flexibility in delaying the initiation of treatment.
9	Lee 2021	Genetic factors	SMN1 Gene Mutations	✓	✓	✓	✓	✓	Spinal muscular atrophy is a progressive disorder characterized by degeneration of spinal cord and brainstem motor

#	Study **ID**	**Prognostic factor**	**Characteristics**	**Relevance for**					**Details**
				Pre-symptomatic 1/2 SMN2 copies	**Pre-symptomatic 3 SMN2 copies**	**SMA Type I**	**SMA Type II**	**SMA Type III**	
									neurons caused by homozygous deletions in the SMN1 gene, resulting in loss of SMN protein.
		SMN2 copy number	SMN2 copy number	✓	✓	✓	✓	✓	Furthermore, early dosing appears to be critically important, and therefore consensus expert opinion recommends treatment of patients with two or three copies of SMN2 as soon as possible, including those who are presymptomatic and identified via newborn screening programs.
		Pre-symptomatic/symptomatic at treatment initiation	Pre-symptomatic/ symptomatic at treatment initiation	✓	✓	✓	✓	✓	Implementation of newborn screening SMA in 33 US states and increased genetic carrier screening have led to an increase in early, presymptomatic diagnosis of SMA.
		Motoric function	CHOP-INTEND score	✓	✓	✓	✓	✓	Scored at the 50th percentile on the AIMS and 40 out of 64 on the CHOP-INTEND.
		Biomarkers	Neurophysiologic Biomarkers	✓	✓	✓	✓	✓	Repeat examination on the day of gene transfer treatment at 37 days of age (CGA of 40 weeks 1 day) revealed absent reflexes, hypotonia and weakness. His ulnar and peroneal CMAP amplitudes had decreased by 85% and 70%, respectively (ulnar, 0.8 mV; peroneal, 1.2 mV).
		Respiratory function	Ventilatory Support	✓		✓	✓		To have mildly increased work of breathing and cough while feeding at 1-month follow-up. At 6 months of age, continued to have intermittent tachypnea with tasks like feeding but has not required additional respiratory support.
		Nutrition	Feeding and Swallowing Issues	✓		✓	✓		A bedside swallow evaluation at 5 months of age demonstrated deep penetration with thin and nectar thick consistencies requiring modification of oral feeding.

#	Study **ID**	**Prognostic factor**	**Characteristics**	**Relevance for**					**Details**
				Pre-symptomatic 1/2 SMN2 copies	**Pre-symptomatic 3 SMN2 copies**	**SMA Type I**	**SMA Type II**	**SMA Type III**	
10	Kichula 2021	SMN2 Copy Number	SMN2 Copy Number	✓	✓	✓	✓	✓	The severity of SMA is largely dependent on the number of copies of the SMN2 gene, a back-up gene to SMN1. Each SMN2 copy produces approximately 10% of the functional SMN protein produced by a single functional SMN1 copy, partially compensating for the disrupted SMN1 genes as SMN protein is essential for life.
		Age Treatment initiation	Age at treatment	✓	✓	✓	✓	✓	The age at which treatment is initiated significantly influences outcomes. Early treatment, especially in presymptomatic infants or those in the early symptomatic stage, leads to better prognoses, including improved survival and achievement of motor milestones. Clinical studies have consistently demonstrated the benefits of early treatment initiation in SMA, before irreversible loss of motor neurons.
		SMA Type	SMA Type	✓	✓	✓	✓	✓	The traditional classification of SMA into types 0, 1, 2, 3, and 4 based on age of onset and maximum motor milestones achieved is less relevant with disease-modifying therapies. A more functional classification into non-sitters, sitters, and walkers is recommended. Historically, SMA was classified into three major phenotypes (SMA types 1, 2, and 3), differentiated by the child's age at symptom onset and maximum motor milestone achieved. SMA types 0 and 4 were added to describe rare congenital and adult-onset forms of SMA, respectively.
		Nutrition	Nutritional support	✓	✓	✓	✓	✓	The requirement for nutritional support before treatment can indicate the severity of SMA and influence the prognosis. Patients needing less support generally have better outcomes. Onasemnogene abeparvovec was found to increase

#	Study **ID**	**Prognostic factor**	**Characteristics**	**Relevance for**					**Details**
				Pre-symptomatic 1/2 SMN2 copies	**Pre-symptomatic 3 SMN2 copies**	**SMA Type I**	**SMA Type II**	**SMA Type III**	
									motor milestone attainment and reduce the need for nutritional support in many patients.
		Respiratory funcion	Ventilatory support	✓	✓	✓	✓	✓	The requirement for respiratory support before treatment can indicate the severity of SMA and influence the prognosis. Patients needing less support generally have better outcomes. Onasemnogene abeparvovec was found to increase motor milestone attainment and reduce the need for respiratory support in many patients.
11	Ziegler 2020	SMN2 Copy Number	SMN2 Copy Number	✓	✓	✓	✓	✓	The number of SMN2 gene copies significantly influences the disease severity and prognosis. More SMN2 copies generally correlate with a milder phenotype and better prognosis.
		Age onset	Age at symptom onset	✓	✓	✓	✓	✓	Earlier onset of symptoms typically indicates a more severe form of the disease, with worse prognosis.
		SMA Type	SMA Type	✓	✓	✓	✓	✓	SMA is categorized into types 1 through 4 based on age at onset and severity. Type 1 (Werdnig-Hoffmann disease) is the most severe, with onset in infancy and typically the worst prognosis. Type 2 and 3 have a later onset and a relatively better prognosis, while Type 4 is adult-onset and usually the least severe.
		Motoric function	Highest motor milestone at baseline	✓	✓	✓	✓	✓	Initial motor function and the progression rate of motor decline are crucial prognostic indicators. Better initial motor function and slower decline are associated with a better prognosis.
		Respiratory function	Ventilatory Support	✓	✓	✓	✓	✓	Respiratory complications are common in SMA, especially in more severe types. The need for ventilatory support is a significant prognostic factor, with those requiring earlier and

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
									more intensive respiratory support having a poorer prognosis.
		Nutrition	Over/Under-nutrition	✓	✓	✓	✓	✓	Poor nutritional status and difficulties in feeding are associated with worse outcomes. Maintaining adequate nutrition is critical for patient management and prognosis.
		Complications	Complications	✓	✓	✓	✓	✓	The presence and severity of complications, such as scoliosis, contractures, and cardiac issues, also influence the prognosis. Effective management of these complications can improve quality of life and outcomes.
12	Mercuri 2018	SMN2 Copy Number	SMN2 Copy Number	✓	✓	✓	✓	✓	The number of SMN2 copies is crucial for determining the severity of SMA. Type 1 SMA patients usually have two SMN2 copies, type 2 and early-onset type 3 SMA patients have three copies, late-onset type 3 patients have four copies, and type 4 patients have four to six copies. This factor is essential for prognosis and therapeutic approaches.
		Genetic factors	SMN1 Gene Mutations	✓	✓	✓	✓	✓	SMA is commonly caused by homozygous deletions of exons 7 and 8 of the SMN1 gene. Other mutations in SMN1 can be found in a small percentage of cases, usually in combination with an SMN1 deletion on the other allele.
		Age onset	Age at symptom onset	✓	✓	✓	✓	✓	The age at which symptoms begin significantly impacts the prognosis. Earlier onset is associated with a more severe disease progression.
		Region	Regional and cultural standards	✓	✓	✓	✓	✓	Studies have shown variations in the carrier frequency of SMN1 deletions among different ethnic groups, with Asians having the highest carrier frequency.
13	Palmer 2022	SMN2 Copy Number	SMN2 Copy Number	✓	✓	✓	✓	✓	The number of copies of the SMN2 gene is a critical determinant of disease severity. Higher SMN2 copy numbers are

#	Study **ID**	**Prognostic factor**	**Characteristics**	**Relevance for**					**Details**
				Pre-symptomatic 1/2 SMN2 copies	**Pre-symptomatic 3 SMN2 copies**	**SMA Type I**	**SMA Type II**	**SMA Type III**	
									generally associated with milder phenotypes and better outcomes. This is because SMN2 can partially compensate for the loss of SMN1 gene function.
		Age onset	Age at symptom onset	✓	✓	✓	✓	✓	Earlier onset of symptoms, particularly before six months of age, is associated with more severe disease (Type 1 SMA) and poorer outcomes. Later onset of symptoms typically correlates with milder forms (Types 2 and 3) and better prognoses.
		Motoric function	Highest motor milestone at baseline	✓	✓	✓	✓	✓	Higher baseline motor function before treatment initiation is associated with better outcomes. This underscores the importance of early intervention.
		Age Treatment initiation	Age at treatment	✓	✓	✓	✓	✓	Early initiation of disease-modifying therapies significantly improves outcomes, particularly in infants with type 1 SMA. Delays in treatment initiation can lead to irreversible motor neuron loss and poorer functional outcomes.
		Complications	Complications			✓	✓	✓	The development of complications such as scoliosis and joint contractures can negatively impact motor function and overall prognosis, especially in patients aged 6-15 years.
14	Hagenacker 2019	Genetic factors	Genetic modifiers	✓	✓	✓	✓	✓	In addition to the molecular genetic confirmation of the diagnosis of 5q-associated SMA, there should be anamnetic evidence of SMA-related deterioration of motor function in the past years or months.
		Motoric function	Motoric function	✓	✓	✓	✓	✓	In addition to the molecular genetic confirmation of the diagnosis of 5q-associated SMA, there should be anamnetic evidence of SMA-related deterioration of motor function in the past years or months.

#	Study **ID**	**Prognostic factor**	**Characteristics**	**Relevance for**					**Details**
				Pre-symptomatic 1/2 SMN2 copies	**Pre-symptomatic 3 SMN2 copies**	**SMA Type I**	**SMA Type II**	**SMA Type III**	
		Comorbidities	Comorbidities			✓	✓	✓	In the context of an individual benefit-risk assessment, the age of the patient and any life-limiting comorbidities, such as severe oncological diseases, should be considered.
		Age Treatment initiation	Early treatment initiation	✓	✓	✓	✓	✓	In general, the indicated treatment with nusinersen should be started as soon as possible after diagnosis of 5q-SMA, regardless of the patient's age, to preserve or improve as many of the patient's remaining motor functions as possible.
15	Cuscó 2024	SMN2 copy number	SMN2 copy number	✓	✓	✓	✓	✓	It is stated that the number of SMN2 copies is the most significant modifier of disease phenotype and has implications for patient stratification in clinical trials and therapeutic approaches.
		SMN2 genotype	Genotype of SMN2	✓	✓	✓	✓	✓	The paper emphasizes the importance of establishing accurate genotype-phenotype correlations to guide treatment decisions and predict disease progression. This is discussed throughout the "Results" and "Discussion" sections, highlighting the role of careful analysis and retesting when discrepancies arise.
		Presymptomatic/ symptomatic at treatment initiation	Presymptomatic vs. symptomatic at the time of disease	✓	✓	✓	✓	✓	The paper provides guidelines specifically for cases identified through neonatal screening. It discusses how asymptomatic patients with various SMN2 copy numbers might be expected to present and suggests actions based on those expectations. For example, a neonate with one SMN2 copy usually presents with congenital SMA, but if they are asymptomatic at birth, this might suggest an error in SMN2 quantification or the presence of a positive modifier variant.

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
		Early diagnosis	Neonatal Screening and Early Diagnosis	✓	✓	✓	✓	✓	The significance of neonatal screening in detecting SMA early, which can critically affect the course of the disease and therapeutic outcomes, is discussed in the "Introduction" and "Discussion" sections. Early diagnosis through screening allows for timely interventions, potentially modifying the disease trajectory significantly.
16	Glascock 2020	SMN2 copy number	SMN2 copy number	✓	✓	✓	✓	✓	All individuals with SMA have a variable copy number SMN2, a paralog of SMN1, that produces low, but essential levels of SMN protein. Copy number of SMN2 correlates inversely with SMA phenotype severity, as greater SMN2 copy number is associated with milder phenotypic presentation.
		SMN2 genotype	Genotype of SMN2	✓	✓	✓	✓	✓	SMA types 1 and 2 represent a large majority of SMA cases and account for the bulk of those who screen positive for SMA and have three or fewer copies of SMN2. Specific Copy Number Associations: "80% of those with SMA type 1 have two or fewer copies of SMN2". "82% of those with SMA type 2 have three copies of SMN2". "96% of those with SMA type 3 have three or four copies of SMN2".
		Support	Support from family	✓	✓	✓	✓	✓	Physicians should instruct parents/caregivers to contact them immediately if they see any of the following: significant change in child's movement, feeding, or breathing pattern, change in voice/weak cry, increased fatigue without increased activity, trouble feeding in young children or infants, decline or loss of function in previously attained

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
									motor ability or failure to show progress in expected motor ability, abdominal breathing, failure to thrive.
17	Kölbel 2022	Age onset	Age at symptom onset	✓	✓	✓	✓	✓	The age at which symptoms begin is critical in determining the severity of SMA. The classification includes SMA types 0 through 4, with earlier onset generally indicating more severe disease.
		Motoric function	Highest motor milestone at baseline	✓	✓	✓	✓	✓	The highest motor milestone achieved (such as the ability to sit or walk) is used to classify and predict the severity of SMA.
		SMN2 copy number	SMN2 copy number	✓	✓	✓	✓	✓	The number of SMN2 gene copies is a genetic factor that influences disease severity. Fewer copies are associated with more severe forms of SMA .
		Respiratory function	Ventilatory Support	✓		✓	✓		Respiratory insufficiency and the need for ventilation support are significant prognostic indicators. SMA1 patients often require invasive ventilation early on, while SMA2 and some SMA3 patients may need non-invasive ventilation.
		Contractures	Contractures	✓		✓	✓	✓	The presence of joint contractures, which often require surgical intervention, is common in more severe forms of SMA.
		Genetic factors	Genetic modifiers	✓	✓	✓	✓	✓	Rare variants in the SMN2 gene and other positive SMN-independent genetic modifiers can influence the phenotype and are considered in prognosis.
18	Nennstiel 2022	Age onset	Age at symptom onset	✓	✓	✓	✓	✓	The age at which symptoms first appear is critical. Early onset, especially within the first few weeks of life, is associated with a more severe form of the disease (SMA type I) and a higher risk of mortality within the first two years of life if untreated.

#	Study ID	Prognostic factor	Characteristics	Relevance for					Details
				Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic 3 SMN2 copies	SMA Type I	SMA Type II	SMA Type III	
		SMA Type	SMA Type	✓	✓	✓	✓	✓	SMA is traditionally classified into five types based on motor skills achieved. The classification includes type 0 (most severe), type I (severe infantile form), type II, type III, and type IV (mildest). A more pragmatic classification into "non-sitter," "sitter," and "walker" is also used. The specific type impacts prognosis significantly.
		Respiratory function	Ventilatory Support	✓	✓	✓	✓	✓	The involvement of respiratory muscles and the need for mechanical ventilation are crucial prognostic factors. Severe respiratory muscle weakness often leads to higher mortality.
		Pre-symptomatic/ symptomatic at treatment initiation	Pre-symptomatic/ symptomatic at treatment initiation	✓	✓	✓	✓	✓	Initiating therapy pre-symptomatically has shown significant improvement in motor and respiratory outcomes. Drugs for SMN2 gene modification or SMN1 gene replacement have dramatically improved prognosis.
		Early diagnosis	Time between diagnosis and start of treatment	✓	✓	✓	✓	✓	Early diagnosis and intervention allow for the prompt initiation of treatment, which can prevent motor regression and early mortality.
		Genetic factors	SMN1 Gene Mutations	✓	✓	✓	✓	✓	The disease is caused by genetic defects in the SMN1 gene on chromosome 5. Most cases are due to a homozygous deletion of the SMN1 gene.
		SMN2 copy number	SMN2 copy number	✓	✓	✓	✓	✓	The more SMN2 copies are present, the more likely it is that the disease will start later and have a milder course.
19	Ludolph 2021	Genetic factors	SMN1 Gene Mutations	✓	✓	✓	✓	✓	The severity of SMA correlates with mutations in the SMN1 gene on chromosome 5q13.2. A homozygous deletion of exons 7 and 8 or only exon 7 of the SMN1 gene is found in about 94% of patients.

#	Study **ID**	**Prognostic factor**	**Characteristics**	**Relevance for**					**Details**
				Pre-symptomatic 1/2 SMN2 copies	**Pre-symptomatic 3 SMN2 copies**	**SMA Type I**	**SMA Type II**	**SMA Type III**	
		SMN2 copy number	SMN2 copy number	✓	✓	✓	✓	✓	The severity of SMA is inversely related to the number of SMN2 copies, with fewer copies generally correlating with more severe disease.
		SMA Type	SMA Type			✓	✓	✓	SMA is classified into types (0, 1, 2, 3, and 4) based on the maximum motor skills achieved (never-sitting, sitting, walking) and the age of onset. This classification helps in determining the prognosis and expected progression.
20	Finkel 2018	Motoric function	Highest motor milestone at baseline	✓	✓	✓	✓	✓	Patients with more severe loss of muscle function typically have poorer outcomes.
		Respiratory function	Lung function	✓	✓	✓	✓	✓	Respiratory assessment and support should be of highest priority. Management should include proactive measures including optimizing use of bilevel positive airway pressure (i.e., NIV, not CPAP) respiratory support with a backup respiratory rate and augmented secretion clearance prior to empiric oxygen supplementation.
		Nutrition	Nutritional Support	✓	✓	✓	✓	✓	As reported in the Nutritional Care Section, during acute illness, fasting should be avoided to prevent metabolic acidosis, hyper/hypoglycemia or fatty acid metabolism abnormalities.
21	Leitfaden 2017	Age onset	Age at symptom onset	✓	✓	✓	✓	✓	The document explains that the age at which symptoms appear is a critical prognostic factor. SMA type I manifests within the first 6 months of life and is associated with severe symptoms such as inability to sit or roll independently. Conversely, SMA type IV appears in adulthood with milder symptoms.

#	Study **ID**	**Prognostic factor**	**Characteristics**	**Relevance for**					**Details**
				Pre-symptomatic 1/2 SMN2 copies	**Pre-symptomatic 3 SMN2 copies**	**SMA Type I**	**SMA Type II**	**SMA Type III**	
		Motoric function	Highest motor milestone at baseline	✓	✓	✓	✓	✓	Achieving motor milestones is a significant indicator of disease severity. SMA type I patients are unable to sit independently, SMA type II patients can sit but not walk independently, and SMA type III patients can walk but may lose this ability over time.
		SMN2 copy number	SMN2 copy number	✓	✓	✓	✓	✓	The number of SMN2 gene copies strongly influences the disease severity. Generally, a higher number of SMN2 copies correlates with a milder form of the disease. For example, SMA Type I patients typically have 2 copies of the SMN2 gene, whereas SMA Type IV patients may have 4 to 6 copies.
		Respiratory Function	Lung function	✓	✓	✓	✓	✓	Respiratory complications are common and significant prognostic factors in SMA. Regular assessments of lung capacity and monitoring for changes in respiratory function are crucial. Breathing problems, especially in those who cannot sit, can lead to severe health issues.
		Nutrition	Nutritional support	✓	✓	✓	✓	✓	Proper nutritional management and bone health are critical in SMA. Nutritional deficiencies can exacerbate symptoms, and ensuring adequate intake of calcium and vitamin D is essential to prevent osteoporosis. Regular monitoring and tailored nutritional plans are recommended
		Orthotics	Orthotics	✓	✓	✓	✓	✓	Orthopedic complications, such as scoliosis and joint contractures, impact the prognosis of SMA. Regular monitoring and interventions like orthoses or surgical options help maintain mobility and prevent further complications.

Abbreviations: AIMS: Alberta Infant Motor Scale, CMAP: Compound Muscle Action Potential, CPAP: Continuous Positive Airway Pressure, DMT: Disease-Modifying Treatment, FVC: Forced Vital Capacity, MND: Motor Neurone Disease, MI-E: Mechanical Insufflation-Exsufflation, NBS: Newborn Screening, NIV: Non Invasive Ventilation, SMA: Spinal Muscular Atrophy

4. Annex

A1 Annex 1 MEDLINE search strategy

Table 15: Search string for review of guidelines and recommendations

Database	MEDLINE	
Search interface	PubMed	
Search date	02.05.2024	
No	**Search terms**	**Results**
1	((((("Muscular Atrophy, Spinal"[mh] OR "Motor Neuron Disease"[mh:noexp]) OR (motor[Title/Abstract] AND neuron*[Title/Abstract] AND disease*[Title/Abstract])) OR (spinal[tiab] OR bulbo-spinal[tiab] OR bulbospinal[tiab] OR myelopath*[tiab] OR progressiv*[tiab] OR spinobulbar[tiab] AND (muscular[tiab] OR muscle[tiab]) AND atroph*[tiab])) OR ((spinal[tiab] OR (neurogenic scapuloperonea*[tiab])) AND amyotroph*[tiab])) OR ((Spinal[tiab] OR bulbo-spinal[tiab] OR bulbospinal[tiab] OR spinobulbar[tiab] OR spinopontin*[tiab] OR (hereditary motor[tiab])) AND neuronopath*[tiab])	44,943
2	(#1) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title])	112
3	(#1) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title]) Filters: from 2015 - 2024	52

Table 16: Search string for review of systematic reviews and meta-analyses

Database	MEDLINE	
Search interface	PubMed	
Search date	02.05.2024	
No	**Search terms**	**Results**
1	((("muscular atrophy, spinal"[MeSH Terms]) OR (("spinal"[Title/Abstract] OR "bulbo-spinal"[Title/Abstract] OR "bulbospinal"[Title/ Abstract] OR "myelopath*"[Title/Abstract] OR "progressiv*"[Title/Abstract] OR "spinobulbar"[Title/Abstract]) AND ("muscular"[Title/Abstract] OR "muscle"[Title/Abstract]) AND "atroph*"[Title/Abstract])) OR (("spinal"[Title/Abstract] OR "neurogenic scapuloperonea*"[Title/Abstract]) AND "amyotroph*"[Title/Abstract])) OR (("spinal"[Title/Abstract] OR "bulbo-spinal"[Title/Abstract] OR "bulbospinal"[Title/ Abstract] OR "spinobulbar"[Title/Abstract] OR "spinopontin*"[Title/Abstract] OR "hereditary motor"[Title/Abstract]) AND "neuronopath*"[Title/Abstract])	19,732
2	(#1) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review[ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri*[tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication[tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab])) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))	457

3	#2 Filters: from 2015 - 2024	356
4	(#3) NOT "The Cochrane database of systematic reviews"[Journal]	350

A2 Annex 2 Cochrane search strategy

Table 17: Search string for review of systematic reviews and meta-analyses

Database	Cochrane Database of Systematic Reviews	
Search interface	Cochrane Library	
Search date	02.05.2024	
No	**Search terms**	**Results**
1	[mh "spinal muscular atrophy"]	148
2	[mh "motor neuron disease"]	1,113
3	(motor NEXT neuron* NEXT disease*):ti,ab,kw	605
4	(spinal OR "bulbo spinal" OR bulbospinal OR myelopath* OR progressiv* OR spinobulbar):ti,ab,kw AND (Muscular OR muscle):ti,ab,kw AND (Atroph*):ti,ab,kw	712
5	(Spinal OR (neurogenic NEXT scapuloperonea*)):ti,ab,kw AND (Amyotroph*):ti,ab,kw	174
6	(Spinal OR "bulbo spinal" OR bulbospinal OR spinobulbar OR spinopontin* OR "hereditary motor"):ti,ab,kw AND (Neuronopath*):ti,ab,kw	2
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	1893
	#7 with Cochrane Library publication date from Jun 2015 to Jun 2024, in Cochrane Reviews	34

A3 Annex 3 Free-hand search – Guidelines and recommendations

Table 18: Guideline databases and selected websites for hand-search

Guideline databases
AWMF Guidelines
CMA Infobase: (CPGs) – Clinical Practice Guidelines Database
TRIP Database
Selected websites of German and international professional societies
Gesellschaft für Neuropädiatrie
Deutsche Gesellschaft für Muskelkranke e.V.
Treat NMD Neuromuscular Network
SMA Europe
Cure SMA
World Muscle Society
Spinal Muscular Atrophy Foundation
My Care Plus
Muscular Dystrophy UK
NHS - Protocol and Guidelines
NICE Guidelines
Gesellschaft für Neuropädiatrie
Treat-NMD Neuromuscular Network
Deutsche Gesellschaft für Muskelkranke e.V.
Initiative SMA
Schweizerischen Muskelgesellschaft
Neurologienetz
Deutsche Gesellschaft für Humangenetik e.V.
Deutsche Gesellschaft für Kinder-und Jugendmedizine.V.
Deutsche Muskelstiftung
Deutsche Muskelschwund-Hilfe e.V.
Muskeln für Muskeln
Patientenstimme SMA
SMA Europe
Marathon

CTM-Austria
AFM Telethon
European Neuro Muscular Centre
Additional free-hand search & PubMed
PubMed
Google
Google-Scholar

5. Bibliography

Abbas, K. S., Eltaras, M. M., El-Shahat, N. A., Abdelazeem, B., Shaqfeh, M., & Brašić, J. R. (2022). The Safety and Efficacy of Nusinersen in the Treatment of Spinal Muscular Atrophy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Medicina (Kaunas)*, *58*(2). https://doi.org/10.3390/medicina58020213

Abiusi, E., Vaisfeld, A., Fiori, S., Novelli, A., Spartano, S., Faggiano, M. V, Giovanniello, T., Angeloni, A., Vento, G., Santoloci, R., Gigli, F., D'Amico, A., Costa, S., Porzi, A., Panella, M., Ticci, C., Daniotti, M., Sacchini, M., Boschi, I., … Tiziano, F. D. (2023). Experience of a 2-year spinal muscular atrophy NBS pilot study in Italy: towards specific guidelines and standard operating procedures for the molecular diagnosis. *J Med Genet*, *60*(7), 697–705. https://doi.org/10.1136/jmg-2022-108873

AlBalawi, M. M., Castro-Codesal, M., Featherstone, R., Sebastianski, M., ermeer, B., Alkhaledi, B., Bedi, P. K., Abusido, T., & MacLean, J. E. (2022). Outcomes of Long-Term Noninvasive Ventilation Use in Children with Neuromuscular Disease: Systematic Review and Meta-Analysis. *Ann Am Thorac Soc*, *19*(1), 109–119. https://doi.org/10.1513/AnnalsATS.202009-1089OC

Albrechtsen, S. S., Born, A. P., & Boesen, M. S. (2020). Nusinersen treatment of spinal muscular atrophy - a systematic review. *Dan Med J*, *67*(9).

Alhammoud, A., Othman, Y., El-Hawary, R., Mackenzie, W. G., & Howard, J. J. (2021). The impact of scoliosis surgery on pulmonary function in spinal muscular atrophy: a systematic review. *Spine Deform*, *9*(4), 913–921. https://doi.org/10.1007/s43390-021-00302-w

Al-Taie, A., & Köseoğlu, A. (2023). Evaluation of the therapeutic efficacy and tolerability of current drug treatments on the clinical outcomes of paediatric spinal muscular atrophy type 1: A systematic review. *Paediatr Respir Rev*, *48*, 65–71. https://doi.org/10.1016/j.prrv.2023.06.004

Amin, R., MacLusky, I., Zielinski, D., Adderley, R., Carnevale, F., Chiang, J., Côté, A., Daniels, C., Daigneault, P., & Harrison, C. (2017). Pediatric home mechanical ventilation: a Canadian Thoracic Society clinical practice guideline executive summary. *Canadian Journal of Respiratory, Critical Care, and Sleep Medicine*, *1*(1), 7–36.

Anderton, R. S., & Mastaglia, F. L. (2015). Advances and challenges in developing a therapy for spinal muscular atrophy. *Expert Review of Neurotherapeutics*, *15*(8), 895–908.

Angeli, M., Alpantaki, K., is, N., Koutserimpas, C., & Hadjipavlou, A. (2022). The effect of scoliosis surgery on pulmonary function in spinal muscular atrophy patients: review of the literature and a meta-analysis. *Eur Spine J*, *31*(9), 2279–2286. https://doi.org/10.1007/s00586-022-07182-2

Angilletta, I., Ferrante, R., Giansante, R., Lombardi, L., Babore, A., Dell'Elice, A., Alessandrelli, E., Notarangelo, S., Ranaudo, M., & Palmarini, C. (2023). Spinal Muscular Atrophy: An Evolving Scenario through New Perspectives in Diagnosis and Advances in Therapies. *International Journal of Molecular Sciences*, *24*(19), 14873.

Aragon-Gawinska, K., Mouraux, C., Dangouloff, T., & Servais, L. (2023). Spinal Muscular Atrophy Treatment in Patients Identified by Newborn Screening-A Systematic Review. *Genes (Basel)*, *14*(7). https://doi.org/10.3390/genes14071377

Baranello, G., Gorni, K., Daigl, M., Kotzeva, A., Evans, R., Hawkins, N., Scott, D. A., Mahajan, A., Muntoni, F., & Servais, L. (2021). Prognostic Factors and Treatment-Effect Modifiers in Spinal Muscular Atrophy. *Clin Pharmacol Ther*, *110*(6), 1435–1454. https://doi.org/10.1002/cpt.2247

Bedi, P. K., Castro-Codesal, M. L., Featherstone, R., AlBalawi, M. M., Alkhaledi, B., Kozyrskyj, A. L., Flores-Mir, C., & MacLean, J. E. (2018). Long-term Non-Invasive Ventilation in Infants: A Systematic Review and Meta-Analysis. *Front Pediatr*, *6*, 13. https://doi.org/10.3389/fped.2018.00013

Bellai, D. J., & Rae, M. G. (2024). A systematic review of the association between the age of onset of spinal bulbar muscular atrophy (Kennedy's disease) and the length of CAG repeats in the androgen receptor gene. *ENeurologicalSci*, *34*, 100495. https://doi.org/10.1016/j.ensci.2024.100495

Bischof, M., Lorenzi, M., Lee, J., Druyts, E., Balijepalli, C., & Dabbous, O. (2021). Matching-adjusted indirect treatment comparison of onasemnogene abeparvovec and nusinersen for the treatment of symptomatic patients with spinal muscular atrophy type 1. *Curr Med Res Opin*, *37*(10), 1719–1730. https://doi.org/10.1080/03007995.2021.1947216

Calucho, M., Bernal, S., Alías, L., March, F., Venceslá, A., Rodríguez-Álvarez, F. J., Aller, E., Fernández, R. M., Borrego, S., & Millán, J. M. (2018). Correlation between SMA type and SMN2 copy number revisited: an analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. *Neuromuscular Disorders*, *28*(3), 208–215.

Claborn, M. K., Stevens, D. L., Walker, C. K., & Gildon, B. L. (2019). Nusinersen: A Treatment for Spinal Muscular Atrophy. *Ann Pharmacother*, *53*(1), 61–69. https://doi.org/10.1177/1060028018789956

Cobo-Vicente, F., San Juan, A. F., Larumbe-Zabala, E., Estévez-González, A. J., Donadio, M. V. F., & Pérez-Ruiz, M. (2021). Neuromuscular Electrical Stimulation Improves Muscle Strength, Biomechanics of Movement, and Functional Mobility in Children With Chronic Neurological Disorders: A Systematic Review and Meta-Analysis. *Phys Ther*, *101*(10). https://doi.org/10.1093/ptj/pzab170

Coratti, G., Cutrona, C., Pera, M. C., Bovis, F., Ponzano, M., Chieppa, F., Antonaci, L., Sansone, V., Finkel, R., Pane, M., & Mercuri, E. (2021). Motor function in type 2 and 3 SMA patients treated with Nusinersen: a critical review and meta-analysis. *Orphanet J Rare Dis*, *16*(1), 430. https://doi.org/10.1186/s13023-021-02065-z

Cuscó, I., Bernal, S., Blasco-Pérez, L., Calucho, M., Alias, L., Fuentes-Prior, P., & Tizzano, E. F. (2020). Practical guidelines to manage discordant situations of SMN2 copy number in patients with spinal muscular atrophy. *Neurology: Genetics*, *6*(6), e530.

Cuscó, I., Bernal, S., Blasco-Pérez, L., Calucho, M., Alias, L., Fuentes-Prior, P., & Tizzano, E. F. (2024). Practical guidelines to manage discordant situations of SMN2 copy number in patients with spinal muscular atrophy. *Neurol Genet*, *6*(6), e530. https://doi.org/10.1212/nxg.0000000000000530

Darbar, I. A., Plaggert, P. G., Resende, M. B. D., Zanoteli, E., & Reed, U. C. (2011). Evaluation of muscle strength and motor abilities in children with type II and III spinal muscle atrophy treated with valproic acid. *BMC Neurology*, *11*, 1–5.

De Sanctis, R., Pane, M., Coratti, G., Palermo, C., Leone, D., Pera, M. C., Abiusi, E., Fiori, S., Forcina, N., & Fanelli, L. (2018). Clinical phenotypes and trajectories of disease progression in type 1 spinal muscular atrophy. *Neuromuscular Disorders*, *28*(1), 24–28.

Dosi, C., & Masson, R. (2024). The impact of three SMN2 gene copies on clinical characteristics and effect of disease-modifying treatment in patients with spinal muscular atrophy: a systematic literature review. *Front Neurol*, *15*, 1308296. https://doi.org/10.3389/fneur.2024.1308296

Dryden Palmer, K., Tuira, L., Reise, K., Alzadjali, A., & Mckinnon, N. (2022). PP232 [Healthcare systems » Capacity building]: COLLABORATIVE INTERPROFESSIONAL GUIDELINE DEVELOPMENT: ADVANCING CRITICAL CARE FOR CHILDREN WITH SPINAL MUSCULAR ATROPHY AND THEIR FAMILIES. . *Pediatric Critical Care Medicine*, *23*(Supplement 1 11S). https://journals.lww.com/pccmjournal/fulltext/2022/11001/pp232__healthcare_systems___capacity_building__.269.aspx

Erdos, J., & Wild, C. (2022). Mid- and long-term (at least 12 months) follow-up of patients with spinal muscular atrophy (SMA) treated with nusinersen, onasemnogene abeparvovec, risdiplam or combination therapies: A systematic review of real-world study data. *Eur J Paediatr Neurol*, *39*, 1–10. https://doi.org/10.1016/j.ejpn.2022.04.006

Farrar, M. A., Calotes-Castillo, L., De Silva, R., Barclay, P., Attwood, L., Cini, J., Ferrie, M., & Kariyawasam, D. S. (2023). Gene therapy-based strategies for spinal muscular atrophy-an Asia-Pacific perspective. *Mol Cell Pediatr*, *10*(1), 17. https://doi.org/10.1186/s40348-023-00171-5

Farrar, M. A., Park, S. B., Vucic, S., Carey, K. A., Turner, B. J., Gillingwater, T. H., Swoboda, K. J., & Kiernan, M. C. (2017). Emerging therapies and challenges in spinal muscular atrophy. *Annals of Neurology*, *81*(3), 355–368.

Finkel, R. S., Mercuri, E., Meyer, O. H., Simonds, A. K., Schroth, M. K., Graham, R. J., Kirschner, J., Iannaccone, S. T., Crawford, T. O., & Woods, S. (2018). Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care;

medications, supplements and immunizations; other organ systems; and ethics. *Neuromuscular Disorders*, *28*(3), 197–207.

Fujak, A., Raab, W., Schuh, A., Richter, S., Forst, R., & Forst, J. (2013). Natural course of scoliosis in proximal spinal muscular atrophy type II and IIIa: descriptive clinical study with retrospective data collection of 126 patients. *BMC Musculoskeletal Disorders*, *14*, 1–5.

Gavriilaki, M., Moschou, M., Papaliagkas, V., Notas, K., Chatzikyriakou, E., Papagiannopoulos, S., Arnaoutoglou, M., & Kimiskidis, V. K. (2022). Nusinersen in Adults with 5q Spinal Muscular Atrophy: a Systematic Review and Meta-analysis. *Neurotherapeutics*, *19*(2), 464–475. https://doi.org/10.1007/s13311-022-01200-3

Gavriilaki, M., Moschou, M., Papaliagkas, V., Notas, K., Chatzikyriakou, E., Zafeiridou, G., Papagiannopoulos, S., Arnaoutoglou, M., & Kimiskidis, V. K. (2022). Biomarkers of disease progression in adolescents and adults with 5q spinal muscular atrophy: a systematic review and meta-analysis. *Neuromuscul Disord*, *32*(3), 185–194. https://doi.org/10.1016/j.nmd.2021.12.005

Gavriilaki, M., Papaliagkas, V., Stamperna, A., Moschou, M., Notas, K., Papagiannopoulos, S., Arnaoutoglou, M., & Kimiskidis, V. K. (2023). Biomarkers of therapeutic efficacy in adolescents and adults with 5q spinal muscular atrophy: a systematic review. *Acta Neurol Belg*, *123*(5), 1735–1745. https://doi.org/10.1007/s13760-022-02028-6

Glascock, J., Sampson, J., Haidet-Phillips, A., Connolly, A., Darras, B., Day, J., Finkel, R., Howell, R. R., Klinger, K., & Kuntz, N. (2020). Treatment algorithm for infants diagnosed with spinal muscular atrophy through newborn screening. *Journal of Neuromuscular Diseases*, *5*(2), 145–158.

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. (2020). *Konzepte zur Generierung versorgungsnaher Daten und deren Aus wertung zum Zwecke der Nutzenbewertung von Arzneimitteln nach § 35a SGB V*. https://www.iqwig.de/download/a19-43_versorgungsnahe-daten-zum-zwecke-der-nutzenbewertung_rapid-report_v1-1.pdf?rev=184598

Jiang, T., Youn, B., Paradis, A. D., Beckerman, R., Barnieh, L., & Johnson, N. B. (2023). A Critical Appraisal of Matching-Adjusted Indirect Comparisons in Spinal Muscular Atrophy. *Adv Ther*, *40*(7), 2985–3005. https://doi.org/10.1007/s12325-023-02520-2

Kennedy, R. A., Carroll, K., McGinley, J. L., & Paterson, K. L. (2020). Walking and weakness in children: a narrative review of gait and functional ambulation in paediatric neuromuscular disease. *J Foot Ankle Res*, *13*(1), 10. https://doi.org/10.1186/s13047-020-0378-2

Kichula, E. A., Proud, C. M., Farrar, M. A., Kwon, J. M., Saito, K., Desguerre, I., & McMillan, H. J. (2021). Expert recommendations and clinical considerations in the use of onasemnogene abeparvovec gene therapy for spinal muscular atrophy. *Muscle & Nerve*, *64*(4), 413–427.

Kolb, S. J., & Kissel, J. T. (2015). Spinal muscular atrophy. *Neurologic Clinics*, *33*(4), 831–846.

Landfeldt, E., Edström, J., Sejersen, T., Tulinius, M., Lochmueller, H., & Kirschner, J. (2019). Quality of life of patients with spinal muscular atrophy: a systematic review. *European Journal of Paediatric Neurology*, *23*(3), 347–356.

Lee, B. H., Waldrop, M. A., Connolly, A. M., & Ciafaloni, E. (2021). Time is muscle: A recommendation for early treatment for preterm infants with spinal muscular atrophy. *Muscle & Nerve*, *64*(2), 153–155.

Lefebvre, S., Bürglen, L., Reboullet, S., Clermont, O., Burlet, P., Viollet, L., Benichou, B., Cruaud, C., Millasseau, P., & Zeviani, M. (1995). Identification and characterization of a spinal muscular atrophy-determining gene. *Cell*, *80*(1), 155–165.

Lin, C. W., Kalb, S. J., & Yeh, W. S. (2015). Delay in Diagnosis of Spinal Muscular Atrophy: A Systematic Literature Review. *Pediatr Neurol*, *53*(4), 293–300. https://doi.org/10.1016/j.pediatrneurol.2015.06.002

Mercuri, E., Finkel, R. S., Muntoni, F., Wirth, B., Montes, J., Main, M., Mazzone, E. S., Vitale, M., Snyder, B., & Quijano-Roy, S. (2018). Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscular Disorders*, *28*(2), 103–115.

Mercuri, E., Lucibello, S., Perulli, M., Coratti, G., de Sanctis, R., Pera, M. C., Pane, M., Montes, J., de Vivo, D. C., Darras, B. T., Kolb, S. J., & Finkel, R. S. (2020). Longitudinal natural history of type I spinal muscular atrophy: a critical review. *Orphanet J Rare Dis*, *15*(1), 84. https://doi.org/10.1186/s13023-020-01356-1

Meylemans, A., & De Bleecker, J. (2019). Current evidence for treatment with nusinersen for spinal muscular atrophy: a systematic review. *Acta Neurol Belg*, *119*(4), 523–533. https://doi.org/10.1007/s13760-019-01199-z

Michelson, D., Ciafaloni, E., Ashwal, S., Lewis, E., Narayanaswami, P., Oskoui, M., & Armstrong, M. J. (2018). Evidence in focus: Nusinersen use in spinal muscular atrophy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*, *91*(20), 923–933. https://doi.org/10.1212/wnl.0000000000006502

Milligan, J. N., Blasco-Pérez, L., Costa-Roger, M., Codina-Solà, M., & Tizzano, E. F. (2022). Recommendations for Interpreting and Reporting Silent Carrier and Disease-Modifying Variants in SMA Testing Workflows. *Genes (Basel)*, *13*(9). https://doi.org/10.3390/genes13091657

Moore, G. E., Lindenmayer, A. W., McConchie, G. A., Ryan, M. M., & Davidson, Z. E. (2016). Describing nutrition in spinal muscular atrophy: A systematic review. *Neuromuscul Disord*, *26*(7), 395–404. https://doi.org/10.1016/j.nmd.2016.05.005

Nennstiel, U., Genzel-Boroviczény, O., Odenwald, B., Ensenauer, R., Rossi, R., Hoffmann, G. F., Schäfer-Graf, U., Blankenstein, O., Streffing, J., & GPP, J. H. (2020). Neugeborenen-Screening auf angeborene Stoffwechselstörungen, Endokrinopathien,

schwere kombinierte Immundefekte (SCID) und Mukoviszidose. *S2k-Leitlinie. AWMF Nr*, 12–24.

NICE, N. (2016). Motor neurone disease: assessment and management. *NICE Guidel NG42 Methods, Evid Recomm*.

Oliver, D., Radunovic, A., Allen, A., & McDermott, C. (2017). The development of the UK National Institute of Health and Care Excellence evidence-based clinical guidelines on motor neurone disease. *Amyotroph Lateral Scler Frontotemporal Degener*, *18*(5), 313–323. https://doi.org/10.1080/21678421.2017.1304558

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., & Brennan, S. E. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Bmj*, *372*.

Pascual-Morena, C., Martínez-Vizcaíno, V., Cavero-Redondo, I., Martínez-García, I., Moreno-Herráiz, N., Álvarez-Bueno, C., & Saz-Lara, A. (2024). Efficacy of risdiplam in spinal muscular atrophy: A systematic review and meta-analysis. *Pharmacotherapy*, *44*(1), 97–105. https://doi.org/10.1002/phar.2866

Pitarch Castellano, I., Cabrera-Serrano, M., Calvo Medina, R., Cattinari, M. G., Espinosa García, S., Fernández-Ramos, J. A., García Campos, O., Gómez-Andrés, D., Grimalt Calatayud, M. A., Gutiérrez Martínez, A. J., Ibáñez Albert, E., Kapetanovic García, S., Madruga-Garrido, M., Martínez-Moreno, M., Medina Cantillo, J., Melián Suárez, A. I., Moreno Escribano, A., Munell, F., Nascimento Osorio, A., … Vázquez-Costa, J. F. (2022). Delphi consensus on recommendations for the treatment of spinal muscular atrophy in Spain (RET-AME consensus). *Neurologia (Engl Ed)*, *37*(3), 216–228. https://doi.org/10.1016/j.nrleng.2021.07.002

Polido, G. J., de, M., a, M. M. V, Carvas, N., Mendonça, R. H., Caromano, F. A., Reed, U. C., Zanoteli, E., & Voos, M. C. (2019). Cognitive performance of children with spinal muscular atrophy: A systematic review. *Dement Neuropsychol*, *13*(4), 436–443. https://doi.org/10.1590/1980-57642018dn13-040011

Prior, T. W. (2008). Carrier screening for spinal muscular atrophy. *Genetics in Medicine*, *10*(11), 840–842.

Qiao, Y., Chi, Y., Gu, J., & Ma, Y. (2023). Safety and Efficacy of Nusinersen and Risdiplam for Spinal Muscular Atrophy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Brain Sci*, *13*(10). https://doi.org/10.3390/brainsci13101419

Ribero, V. A., Daigl, M., Martí, Y., Gorni, K., Evans, R., Scott, D. A., Mahajan, A., Abrams, K. R., & Hawkins, N. (2022). How does risdiplam compare with other treatments for Types 1-3 spinal muscular atrophy: a systematic literature review and indirect treatment comparison. *J Comp Eff Res*, *11*(5), 347–370. https://doi.org/10.2217/cer-2021-0216

Solé, G., Salort-Campana, E., Pereon, Y., Stojkovic, T., Wahbi, K., Cintas, P., Adams, D., Laforet, P., Tiffreau, V., Desguerre, I., Pisella, L. I., Molon, A., & Attarian, S. (2020). Guidance for the care of neuromuscular patients during the COVID-19 pandemic outbreak from the French Rare Health Care for Neuromuscular Diseases Network.

Rev Neurol (Paris), *176*(6), 507–515. https://doi.org/10.1016/j.neurol.2020.04.004

Stevens, D., Claborn, M. K., Gildon, B. L., Kessler, T. L., & Walker, C. (2020). Onasemnogene Abeparvovec-xioi: Gene Therapy for Spinal Muscular Atrophy. *Ann Pharmacother*, *54*(10), 1001–1009. https://doi.org/10.1177/1060028020914274

Wadman, R. I., van der Pol, W. L., Bosboom, W. M. J., Asselman, F. L., van den Berg, L. H., Iannaccone, S. T., & Vrancken, A. (2020). Drug treatment for spinal muscular atrophy types II and III. *Cochrane Database of Systematic Reviews*, *1*. https://doi.org/10.1002/14651858.CD006282.pub5

Wadman, R. I., van der Pol, W. L., Bosboom, W. M. J., Asselman, F., van den Berg, L. H., Iannaccone, S. T., & Vrancken, A. F. J. E. (2019). Drug treatment for spinal muscular atrophy type I. *Cochrane Database of Systematic Reviews*, *12*.

Wan, H. W. Y., Carey, K. A., D'Silva, A., Vucic, S., Kiernan, M. C., Kasparian, N. A., & Farrar, M. A. (2020). Health, wellbeing and lived experiences of adults with SMA: a scoping systematic review. *Orphanet J Rare Dis*, *15*(1), 70. https://doi.org/10.1186/s13023-020-1339-3

Wang, C. H., Finkel, R. S., Bertini, E. S., Schroth, M., Simonds, A., Wong, B., Aloysius, A., Morrison, L., Main, M., & Crawford, T. O. (2007). Consensus statement for standard of care in spinal muscular atrophy. *Journal of Child Neurology*, *22*(8), 1027–1049.

Wang, M. J., Kang, L., Wang, Y. Z., Yang, B. R., Zhang, C., Lu, Y. F., & Kang, L. (2022). Microglia in motor neuron disease: Signaling evidence from last 10 years. *Dev Neurobiol*, *82*(7), 625–638. https://doi.org/10.1002/dneu.22905

Wijngaarde, C. A., Blank, A. C., Stam, M., Wadman, R. I., van den Berg, L. H., & van der Pol, W. L. (2017). Cardiac pathology in spinal muscular atrophy: a systematic review. *Orphanet J Rare Dis*, *12*(1), 67. https://doi.org/10.1186/s13023-017-0613-5

Wirth, B., Karakaya, M., Kye, M. J., & Mendoza-Ferreira, N. (2020). Twenty-five years of spinal muscular atrophy research: from phenotype to genotype to therapy, and what comes next. *Annual Review of Genomics and Human Genetics*, *21*, 231–261.

Wu, J. W., Pepler, L., Maturi, B., Afonso, A. C. F., Sarmiento, J., & Haldenby, R. (2022). Systematic Review of Motor Function Scales and Patient-Reported Outcomes in Spinal Muscular Atrophy. *Am J Phys Med Rehabil*, *101*(6), 590–608. https://doi.org/10.1097/phm.0000000000001869

Yang, D., Ruan, Y., & Chen, Y. (2023). Safety and efficacy of gene therapy with onasemnogene abeparvovec in the treatment of spinal muscular atrophy: A systematic review and meta-analysis. *J Paediatr Child Health*, *59*(3), 431–438. https://doi.org/10.1111/jpc.16340

Yang, M., Awano, H., Tanaka, S., Toro, W., Zhang, S., Dabbous, O., & Igarashi, A. (2022). Systematic Literature Review of Clinical and Economic Evidence for Spinal Muscular Atrophy. *Adv Ther*, *39*(5), 1915–1958. https://doi.org/10.1007/s12325-022-02089-2

Zhong, Z. J., Zheng, P. M., Dou, H. H., & Wang, J. G. (2023). Adverse events in the treatment of spinal muscular atrophy in children and adolescents with nusinersen: A systematic review and meta-analysis. *Front Pediatr*, *11*, 1152318. https://doi.org/10.3389/fped.2023.1152318

Ziegler, A., Wilichowski, E., Schara, U., Hahn, A., Müller-Felber, W., Johannsen, J., von der Hagen, M., von Moers, A., Stoltenburg, C., & Saffari, A. (2020). Handlungsempfehlungen zur Gentherapie der spinalen Muskelatrophie mit Onasemnogene Abeparvovec–AVXS-101: Konsensuspapier der deutschen Vertretung der Gesellschaft für Neuropädiatrie (GNP) und der deutschen Behandlungszentren unter Mitwirkung des Medizinisch-Wissenschaftlichen Beirates der Deutschen Gesellschaft für Muskelkranke (DGM) e. V. *Der Nervenarzt*, *91*(6).